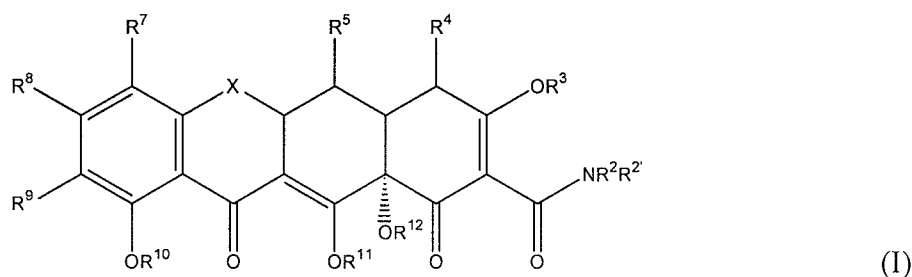


AMENDMENTS TO THE CLAIMSListing of Claims:

This listing of claims will replace all prior versions of the claims and listing of the claims in the application:

1. **(Currently Amended)** A method for treating or preventing malaria in a subject, comprising administering to said subject an effective amount of a substituted tetracycline compound of formula I:



wherein:

X is CR^{6'}R⁶;

R², R^{2'}, R^{4'}, and R^{4''} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R⁴ is NR^{4'}R^{4''}, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R³, R¹¹ and R¹² are each hydrogen, or a pro-drug moiety;

R¹⁰ is hydrogen, or a prodrug moiety;

R⁵ is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R⁶ and R^{6'} are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 is aryl, furanyl, benzofuranyl, thienyl, benzothienyl, indolyl, or pyrrolyl

R^9 is hydrogen; and

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and pharmaceutically acceptable salts thereof, such that malaria is treated or prevented in said subject.

2. **(Canceled)**

3. **(Previously Presented)** The method of claim 1, wherein R^2 , $R^{2'}$, R^3 , R^8 , R^{10} , R^{11} , and R^{12} are hydrogen; R^4 is $NR^{4'}R^{4''}$; $R^{4'}$ and $R^{4''}$ are alkyl, and X is $CR^6R^{6'}$.

4. **(Previously Presented)** The method of claim 3, wherein R^5 , R^6 , and $R^{6'}$ are each hydrogen.

5 - 28. **(Canceled)**

29. **(Currently Amended)** The method of claim 1, wherein R^7 is substituted or unsubstituted phenyl, furanyl, thienyl, or pyrrolyl.

30. **(Currently Amended)** The method of claim 29, wherein R^7 is substituted with halogen, alkoxy, amino, acyl, alkyl, nitro, formyl, amido, ~~alkyl~~, alkenyl, alkynyl, or aryl.

31. **(Currently Amended)** The method of claim 30, wherein R^7 is substituted with ~~is~~-methoxy, ethoxy, propoxy, methylene dioxy, or ethylene dioxy.

32. **(Currently Amended)** The method of claim 30, wherein R^7 is substituted with substituted or unsubstituted methyl, ethyl, propyl, butyl or pentyl.

33. **(Currently Amended)** The method of claim 32, wherein ~~said-substituted or~~ substituted methyl, ethyl, propyl, butyl or pentyl is substituted with an amino, carbocyclic or heterocyclic group.

34. **(Previously Presented)** The method of claim 30, wherein R^7 is substituted with acetyl.

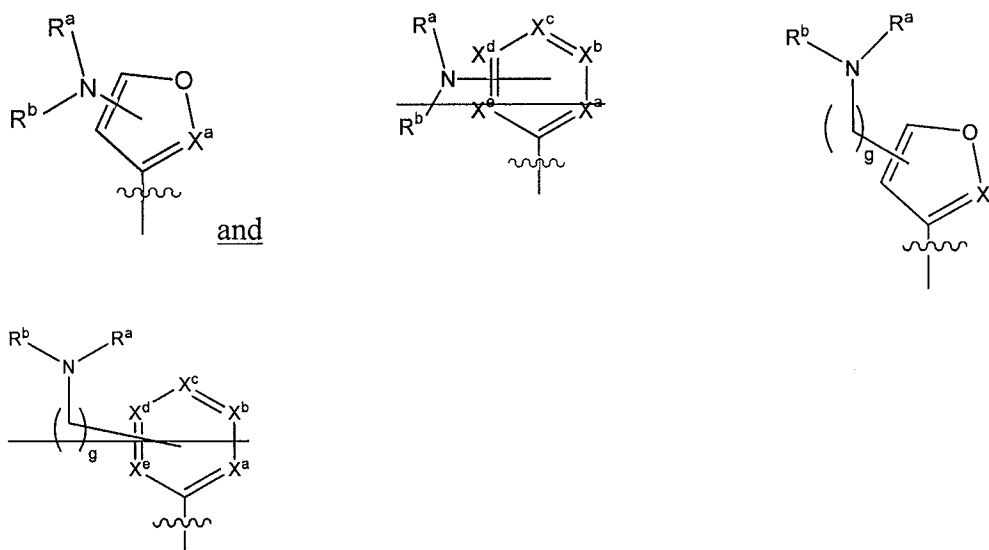
35. **(Currently Amended)** The method of claim ~~28~~1, wherein R⁷ is substituted or unsubstituted ~~heteroaryl~~benzofuranyl, benzothienyl, or indolyl.

36. **(Currently Amended)** The method of claim ~~35~~1, wherein R⁷ is thienyl, ~~imidazolyl, pyrrolyl, pyrrolyl, pyridinyl, or furanyl, pyrimidinyl, or benzofuranyl~~.

37 – 41. **(Canceled)**

42. **(Previously Presented)** The method of claim 1, wherein R⁷ comprises an ionizable nitrogen atom.

43. **(Currently Amended)** The method of claim 1, wherein R⁷ is selected from the group consisting of:



wherein:

R^a and R^b are each independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, or heterocyclic;

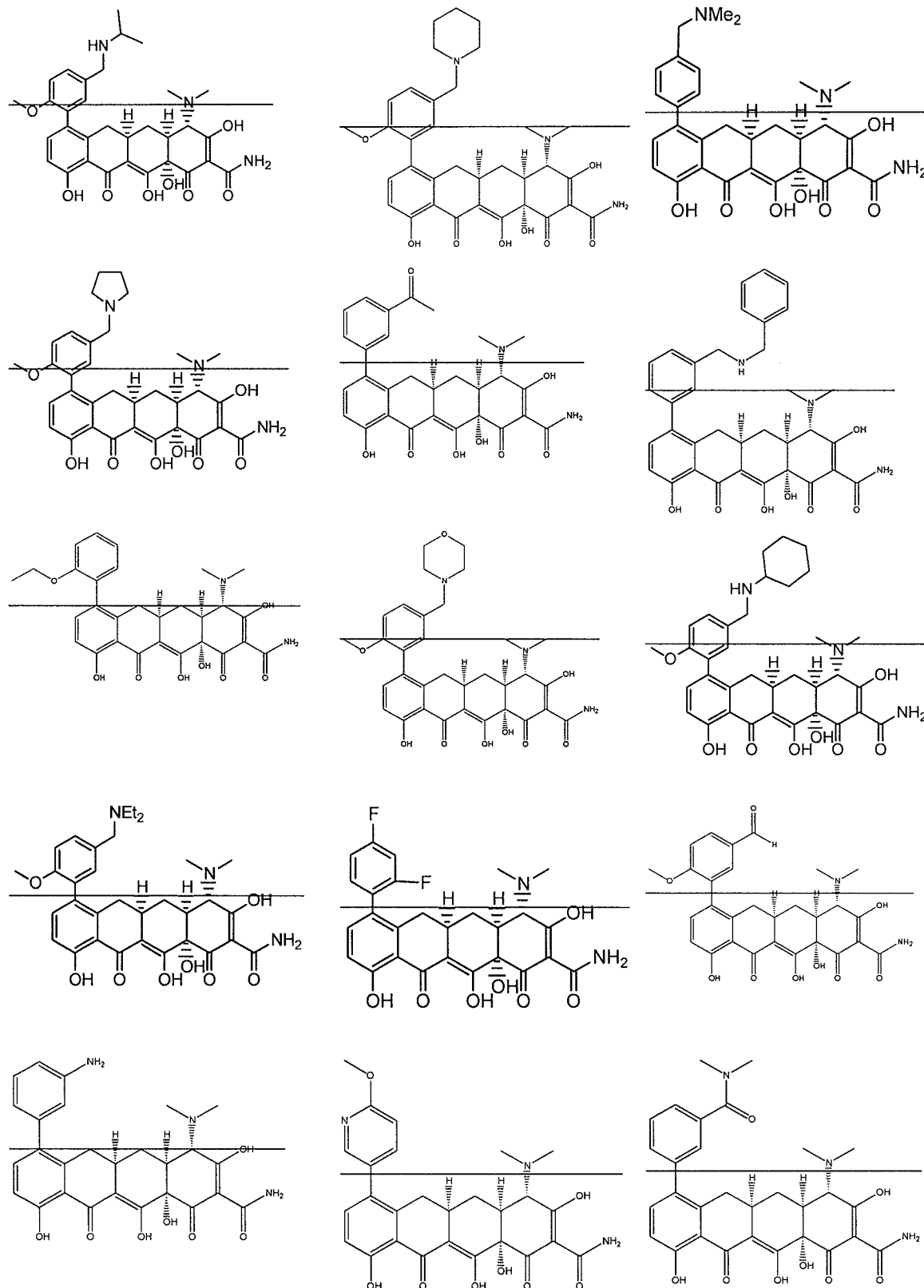
g is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

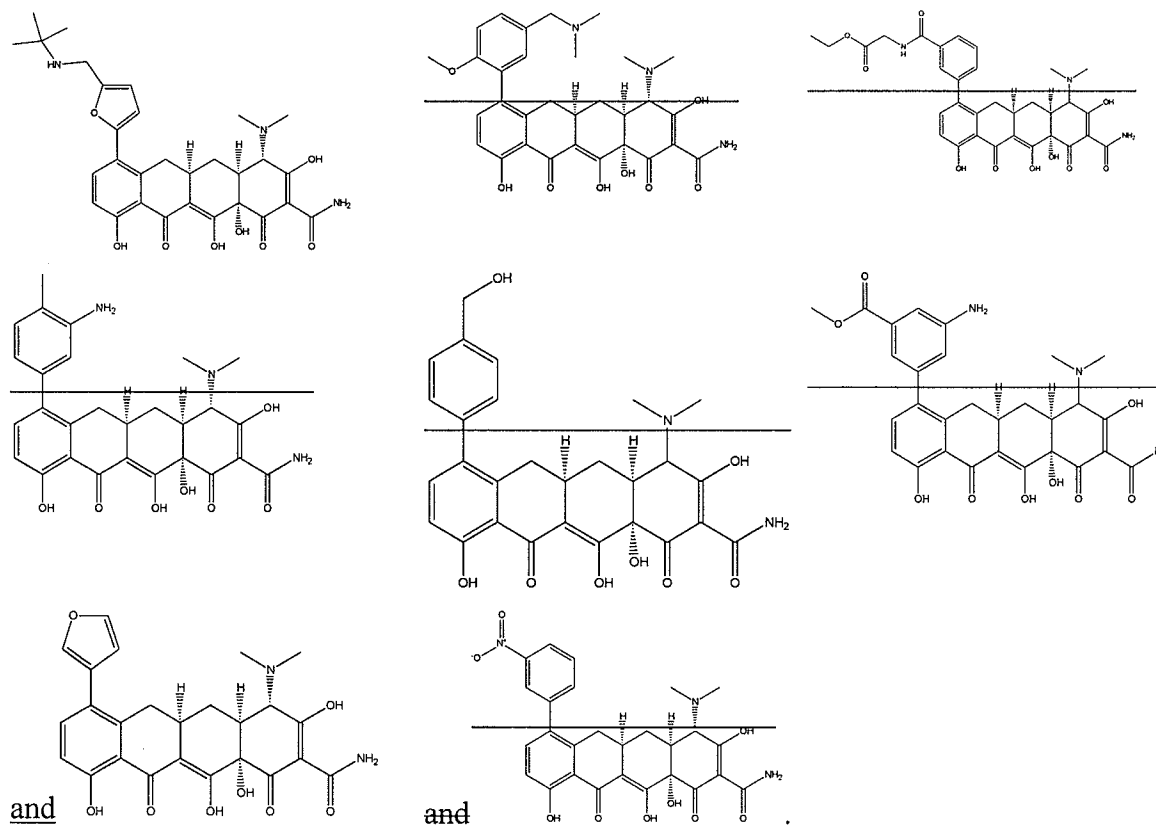
n is 0, 1, 2, or 3; and

X^a, X^b, X^c, X^d, and X^e are each independently optionally substituted carbon, ~~oxygen, nitrogen, or sulfur~~.

44 – 48. **(Canceled)**

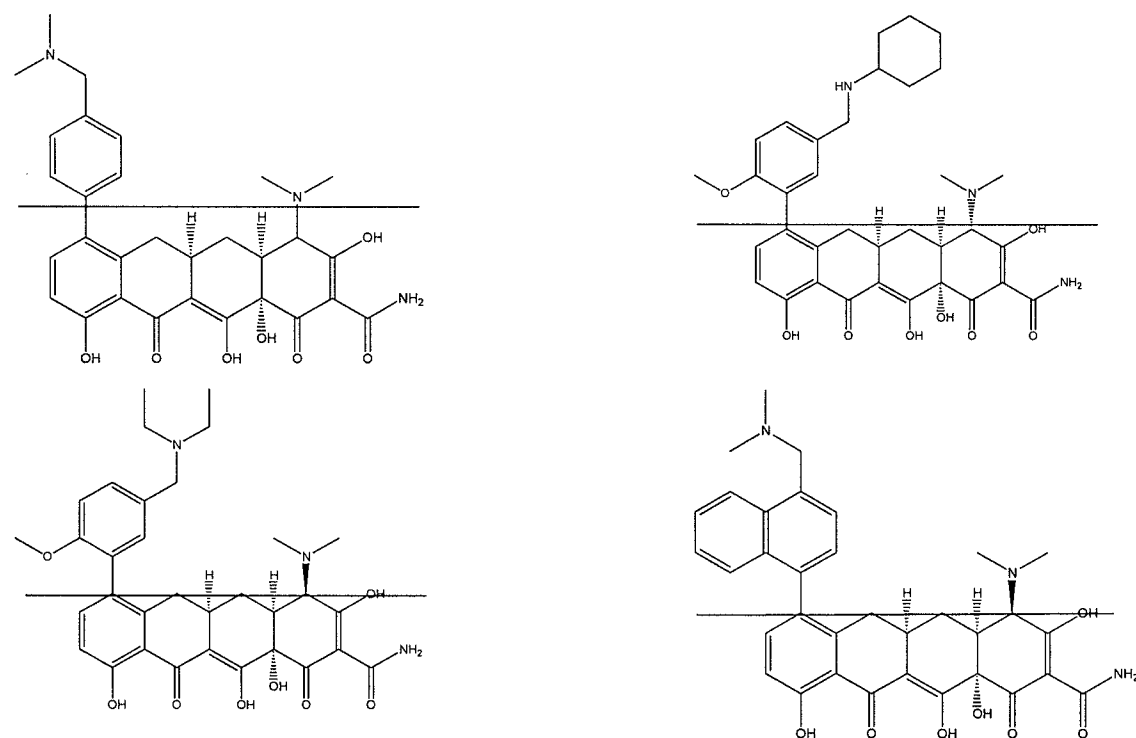
49. **(Currently Amended)** The method of claim 1, wherein said compound is selected from the group consisting of:

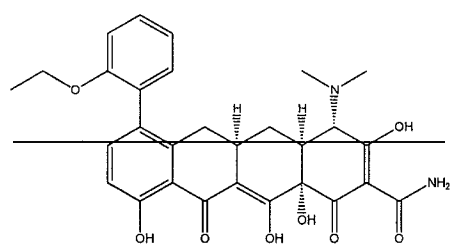
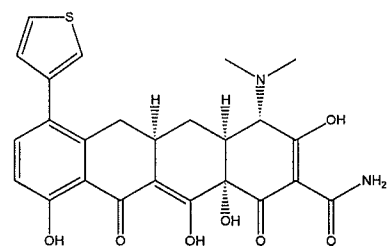
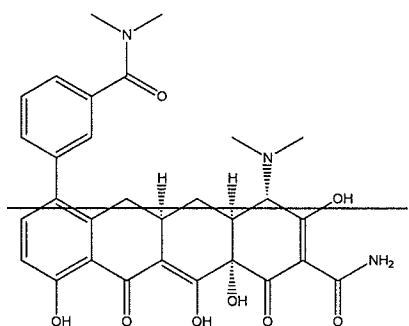
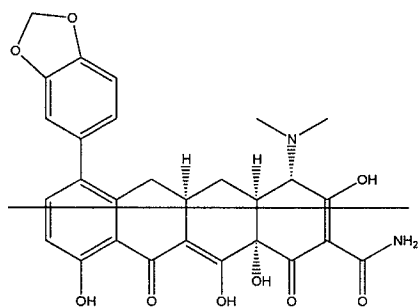
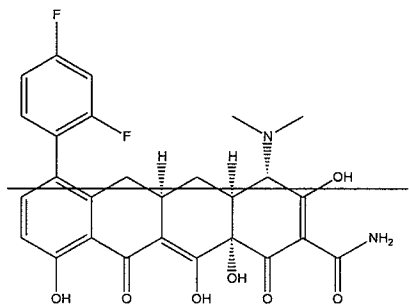
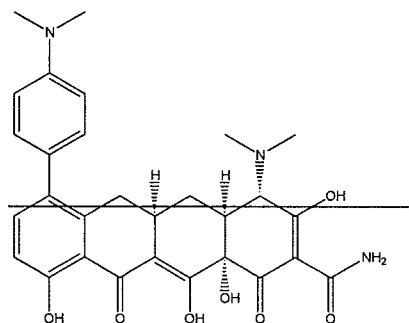
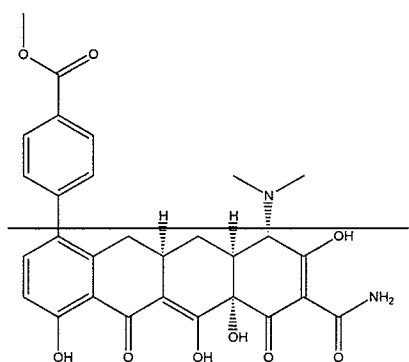
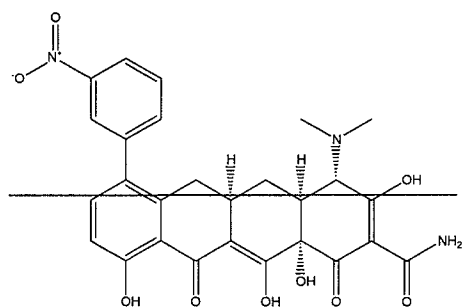
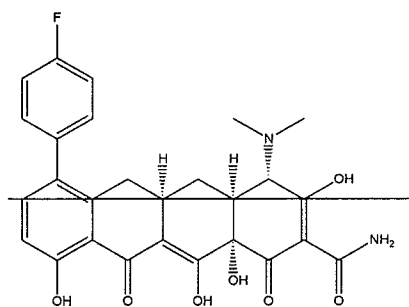
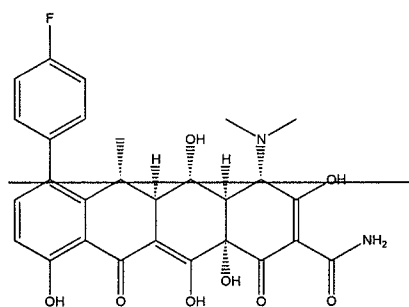


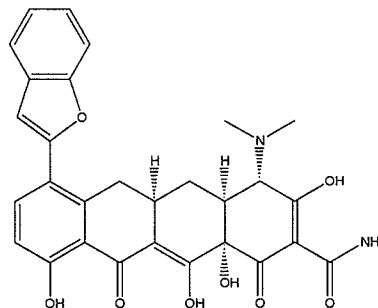
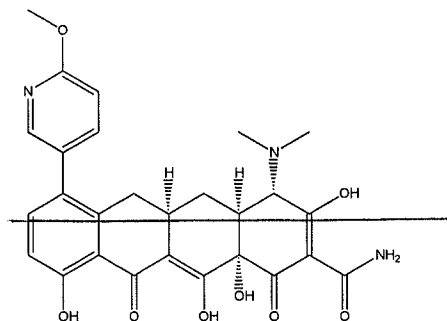
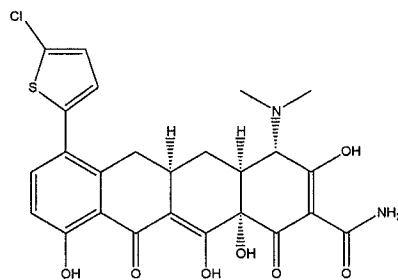
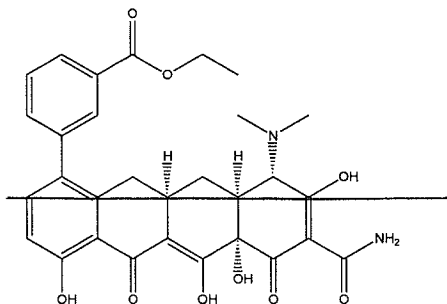
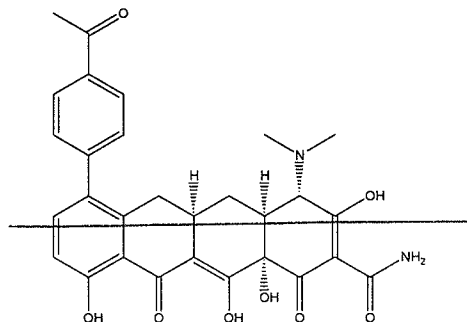
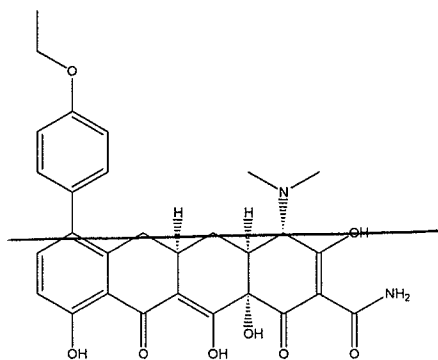
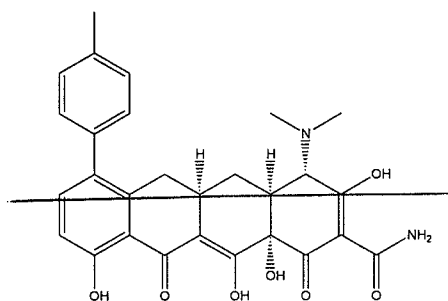
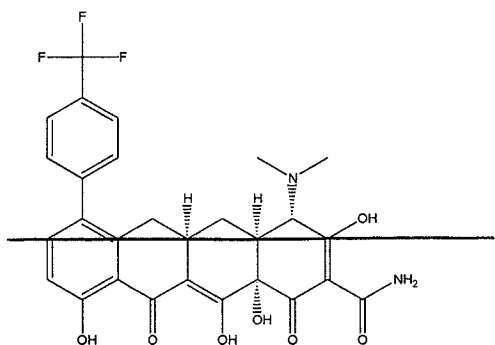
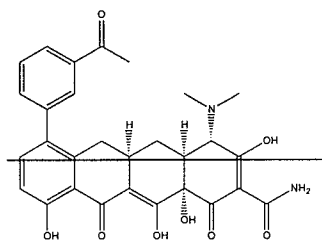
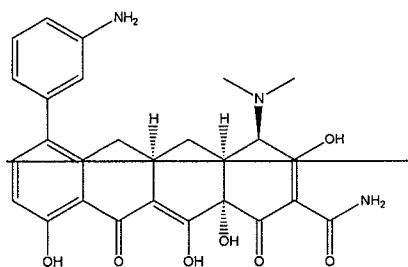


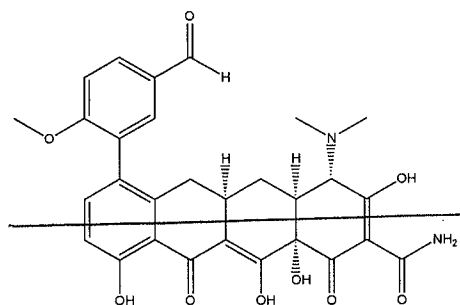
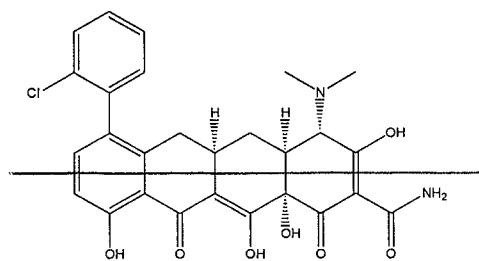
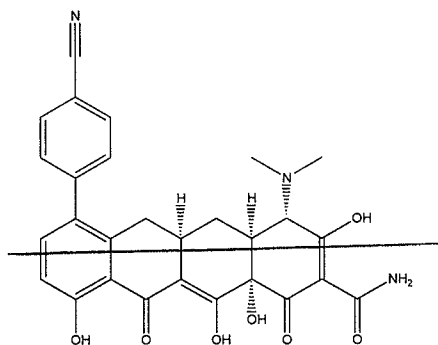
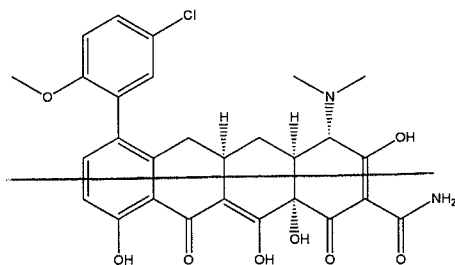
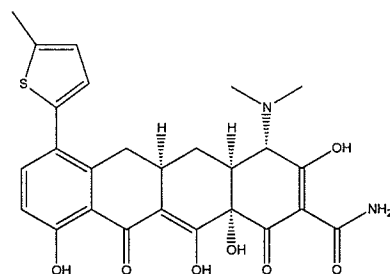
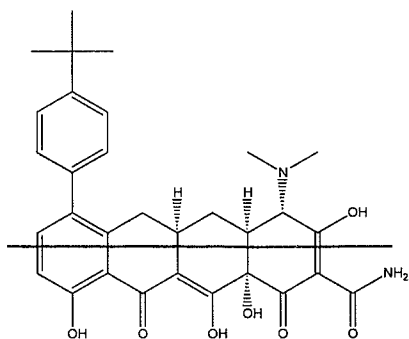
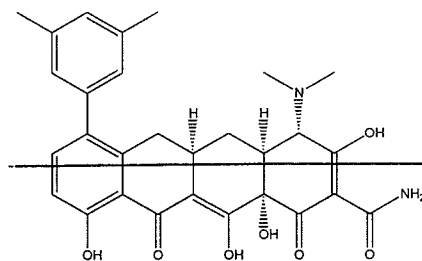
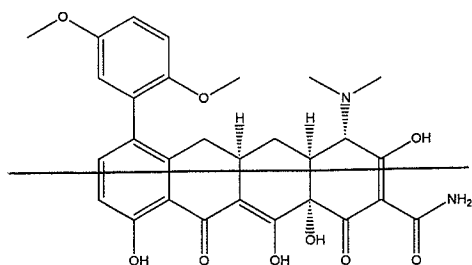
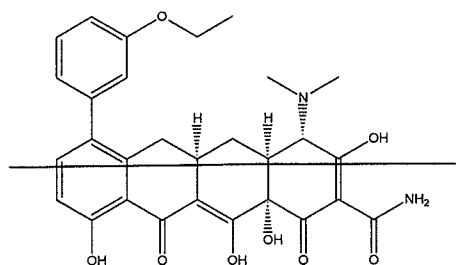
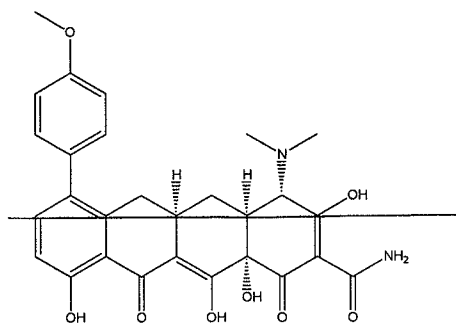
50. **(Currently Amended)** The method of claim 1, wherein said compound is selected from the group consisting of:

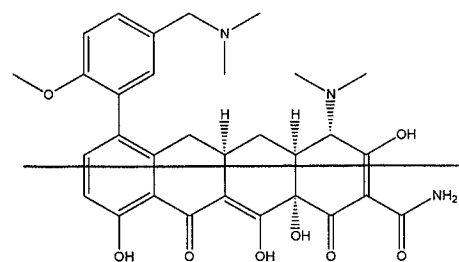
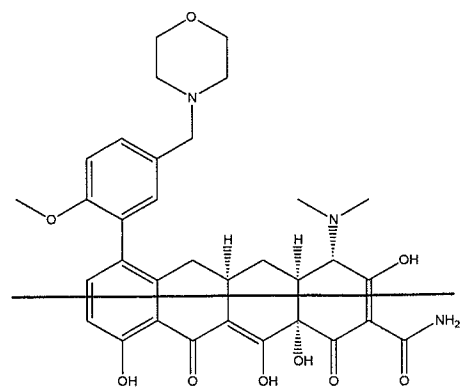
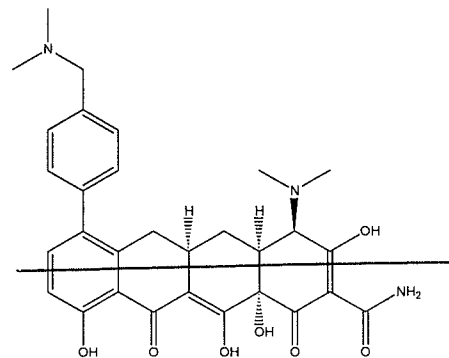
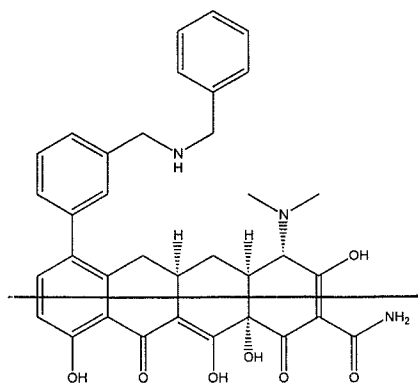
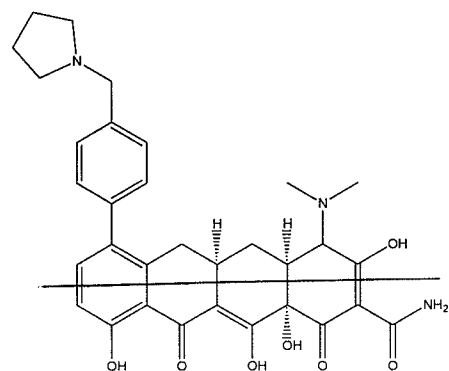
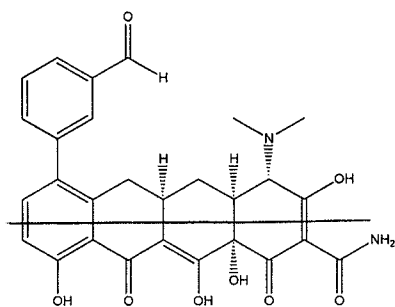
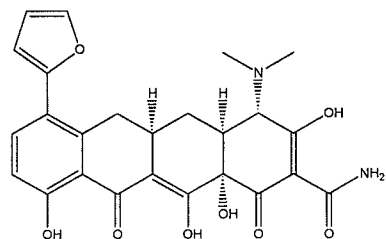
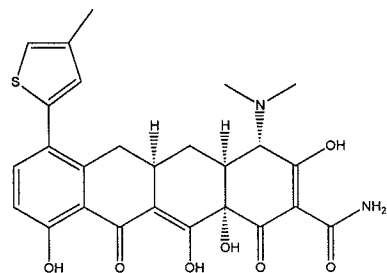
The method of claim 1, wherein said compound is

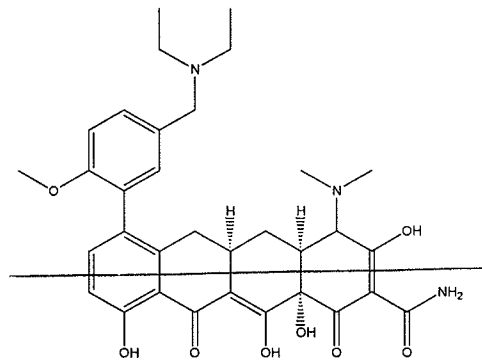
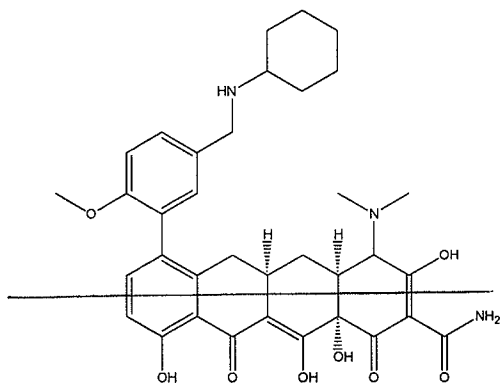
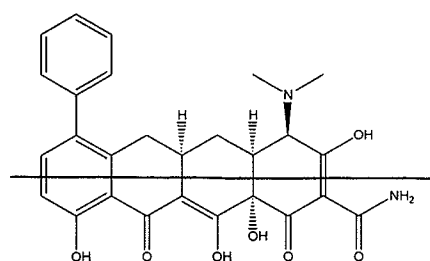
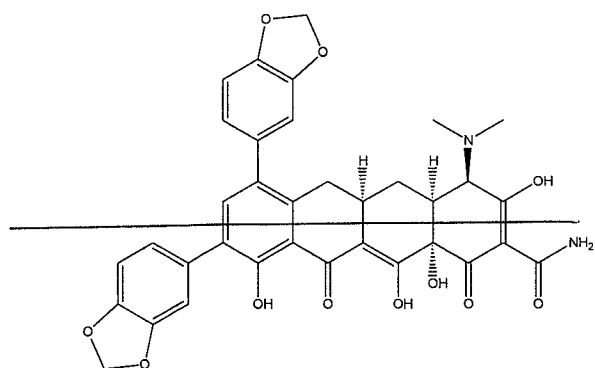
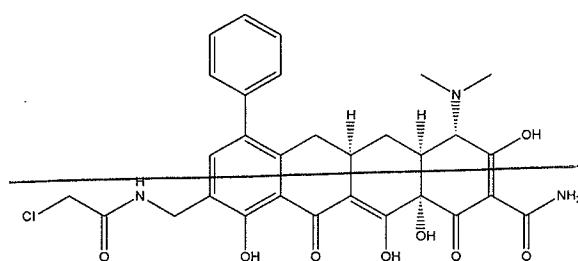
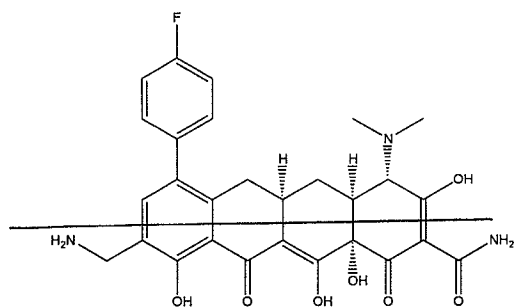
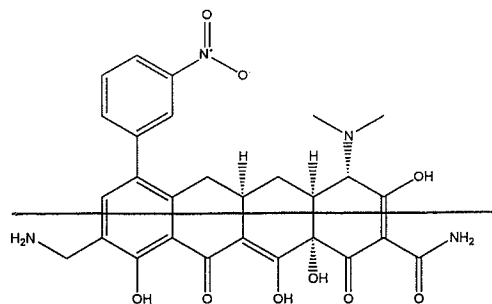
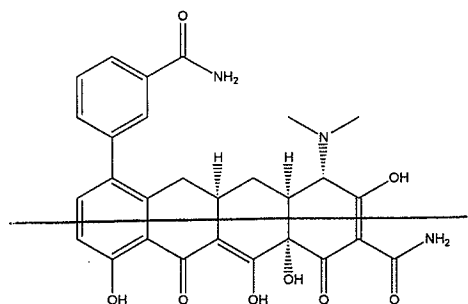


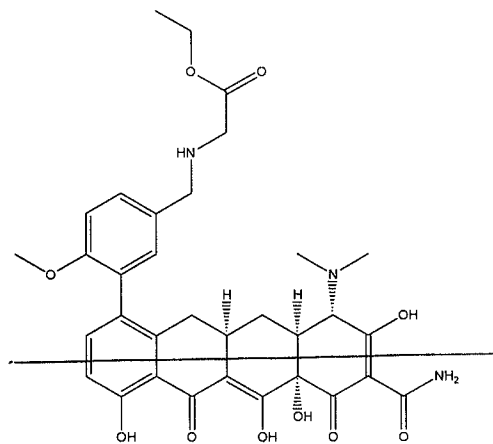
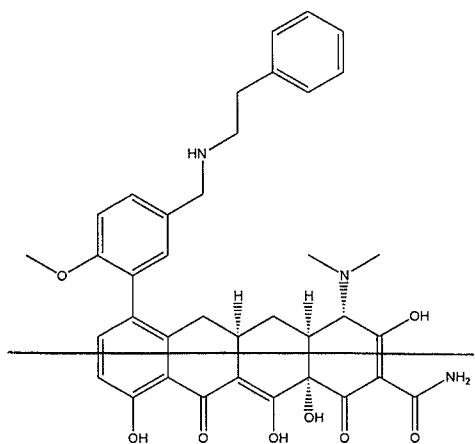
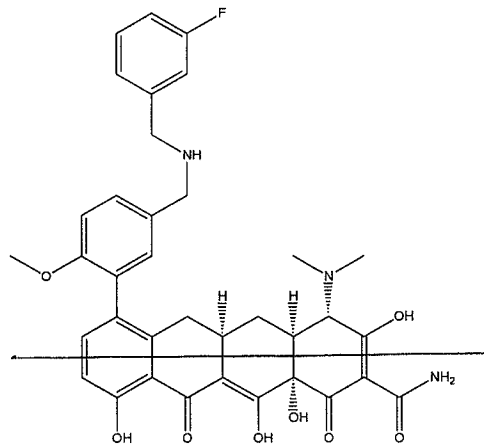
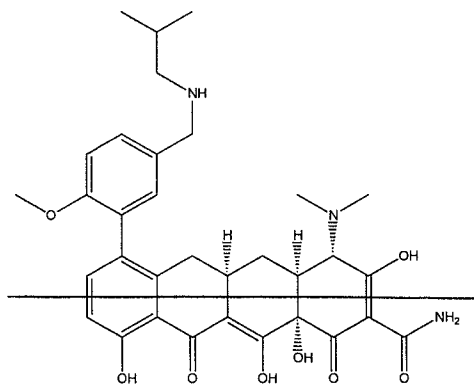
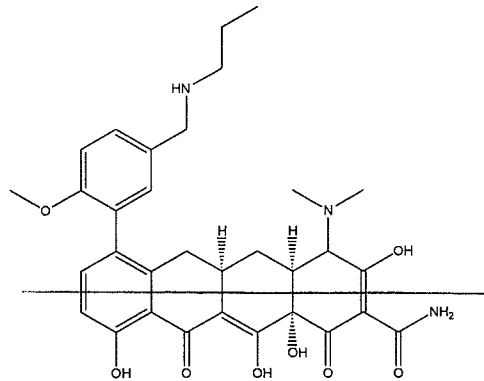
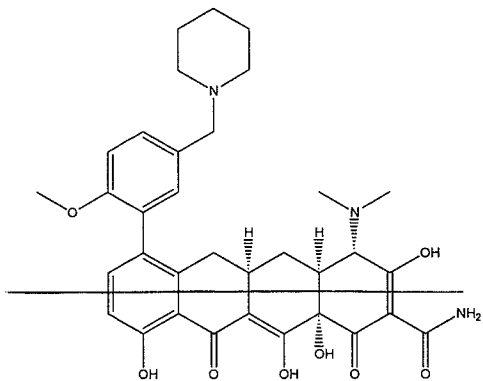
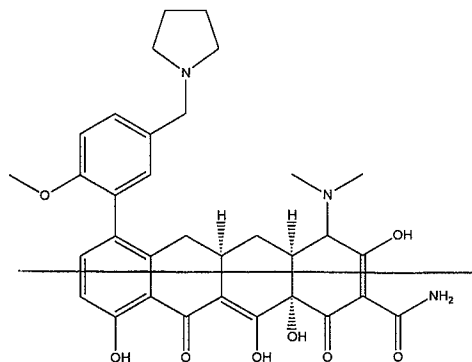
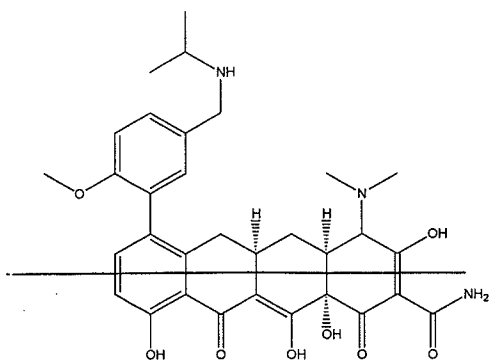


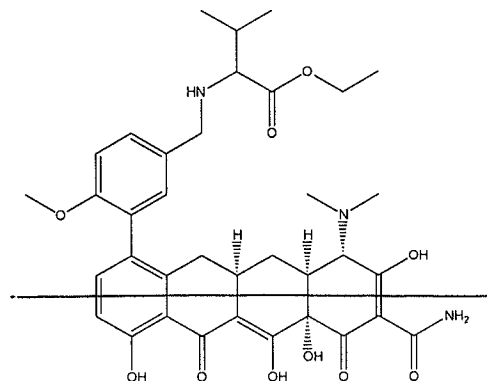
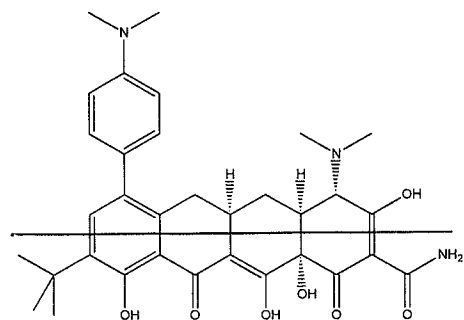
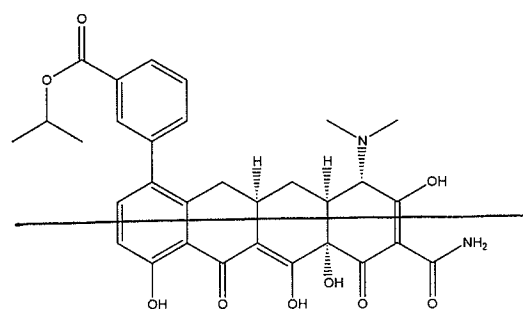
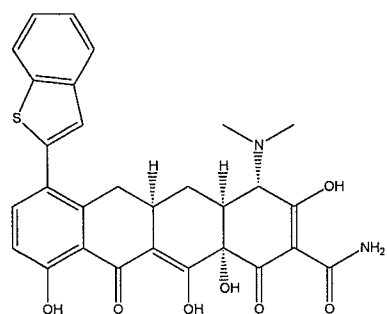
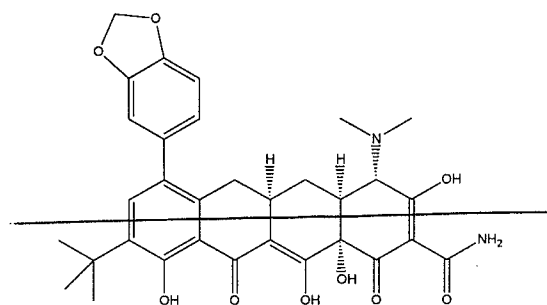
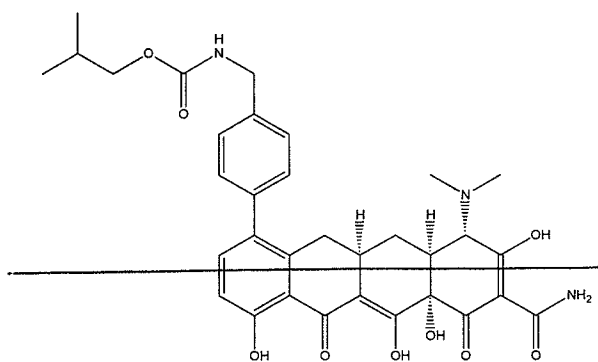
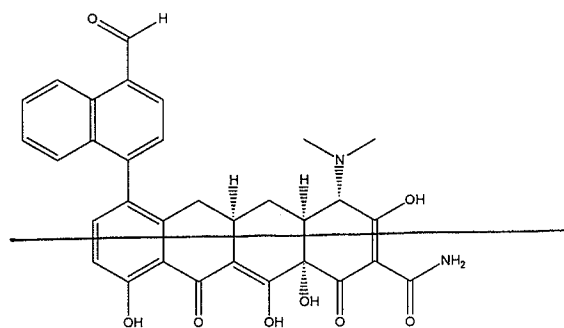
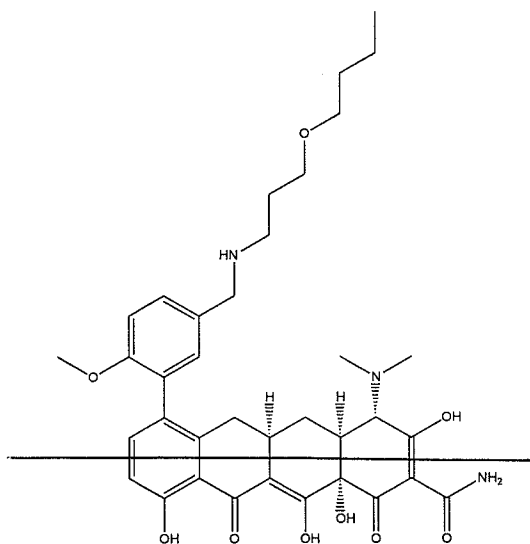


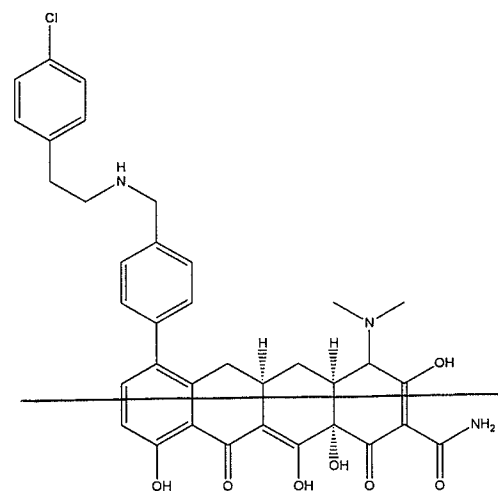
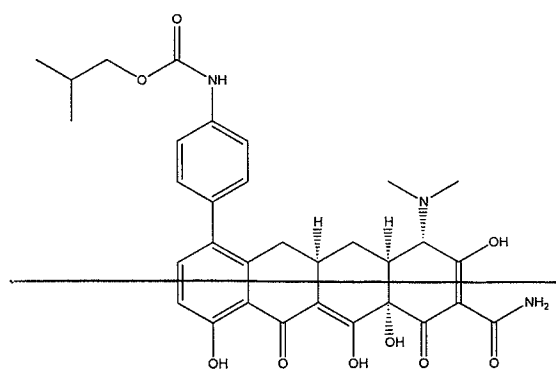
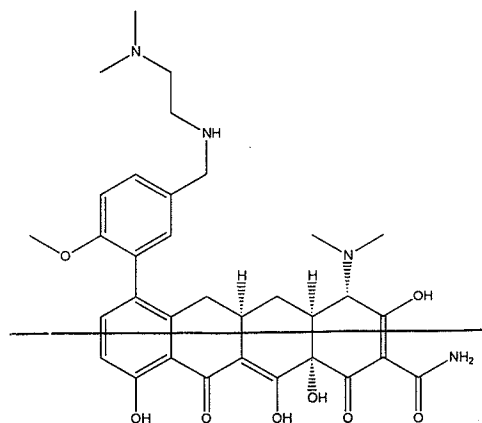
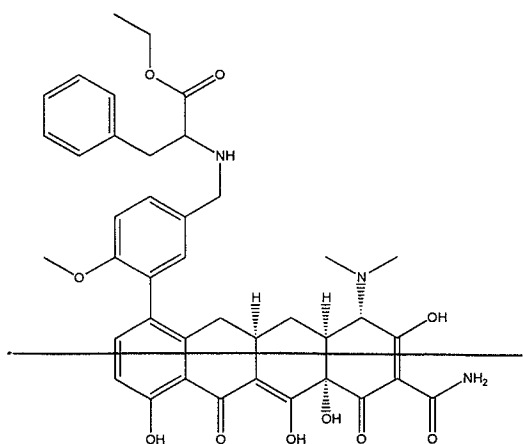
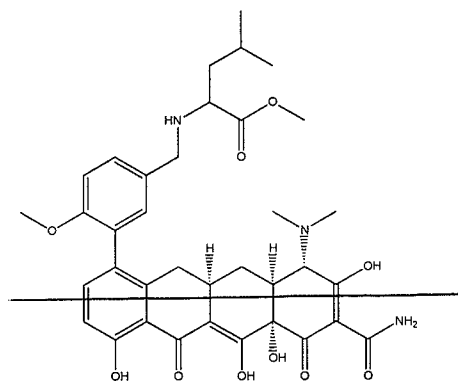
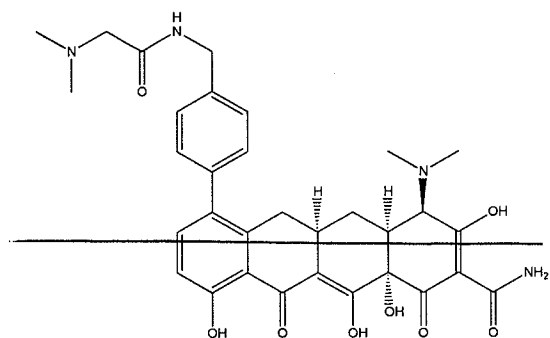


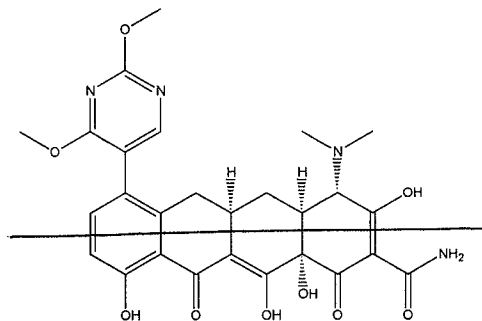
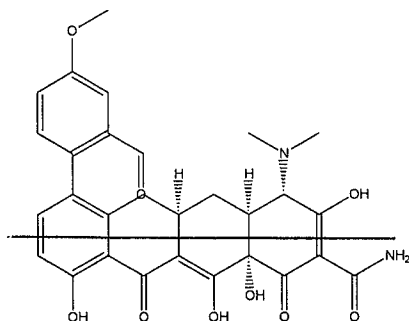
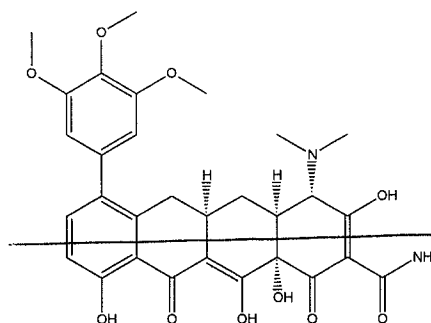
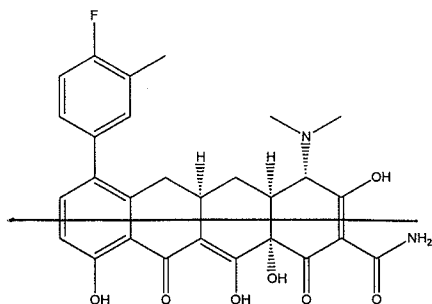
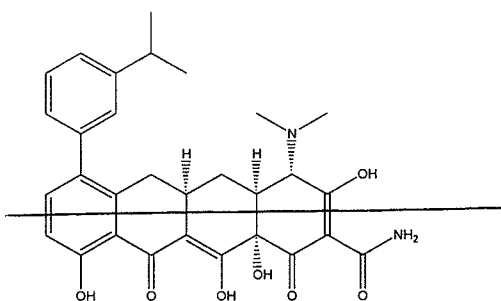
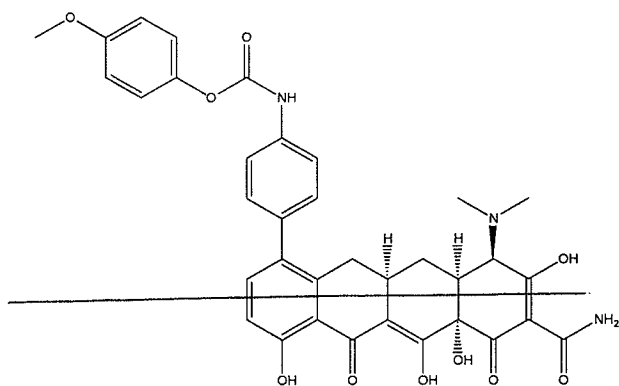
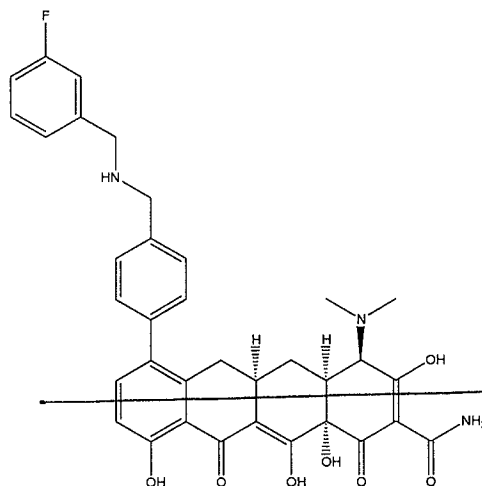
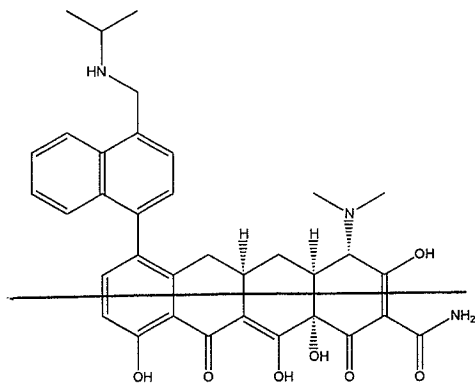


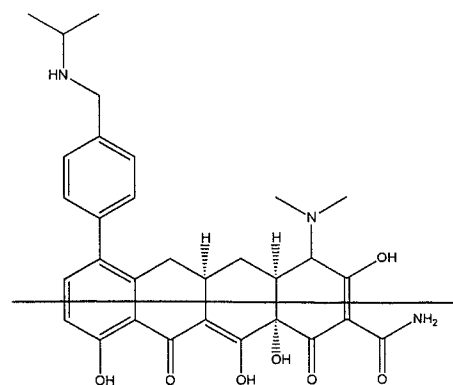
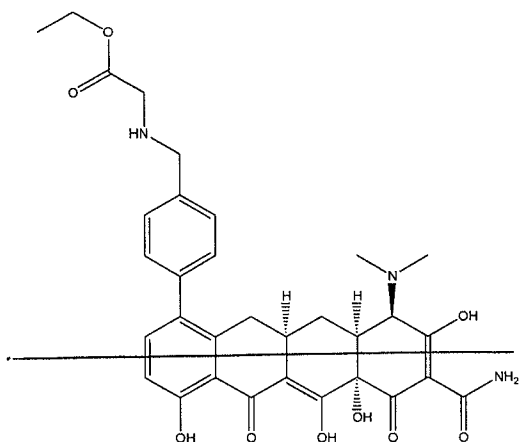
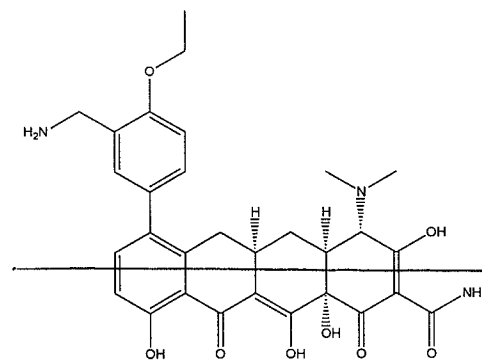
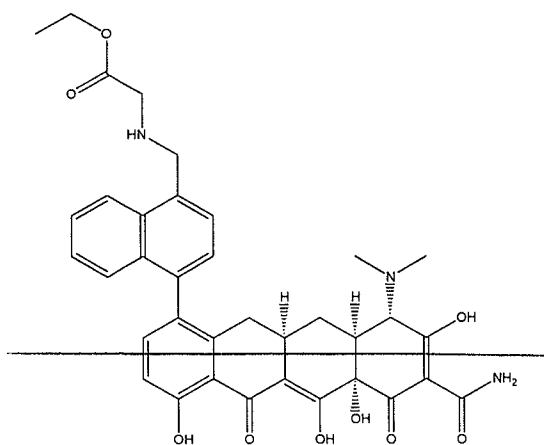
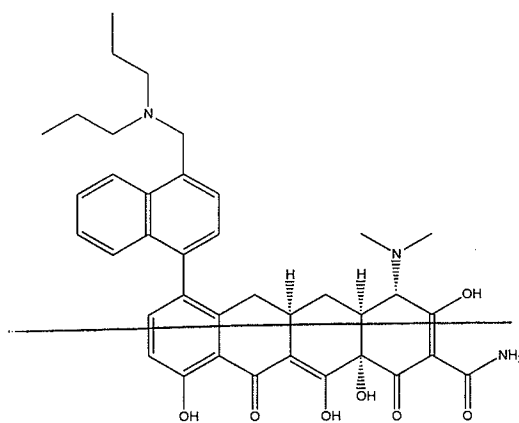
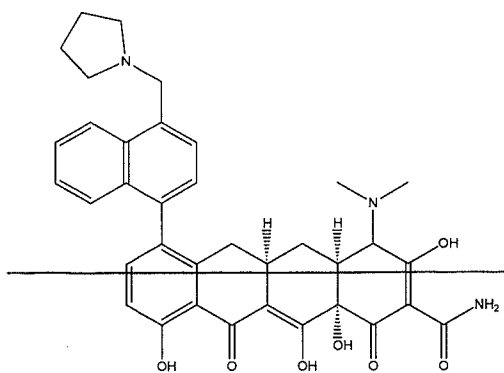
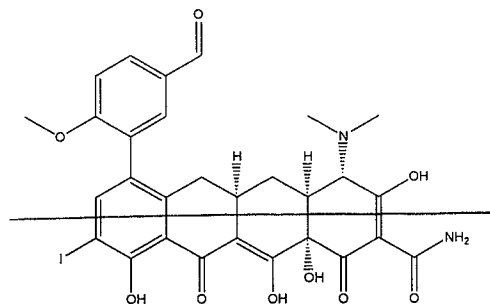
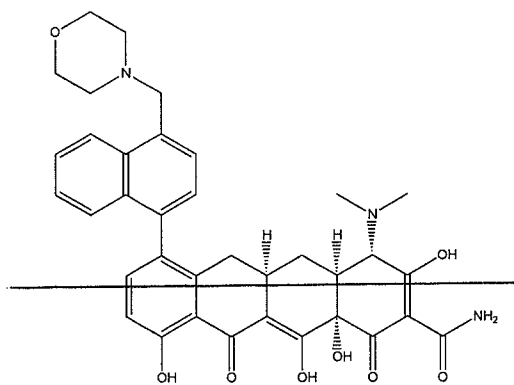


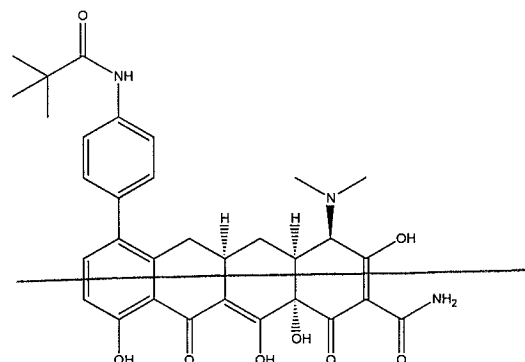
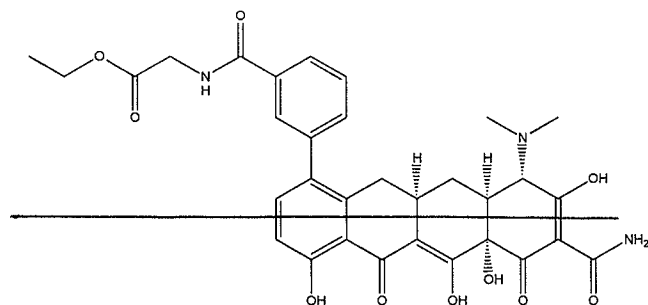
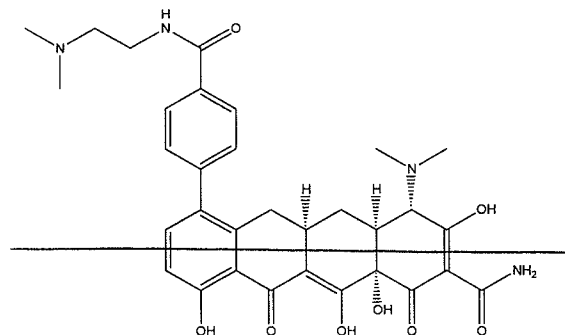
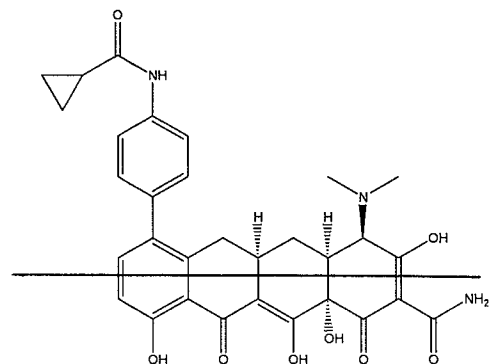
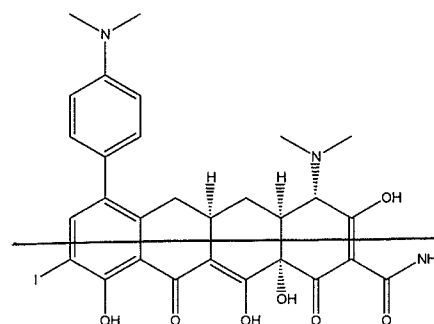
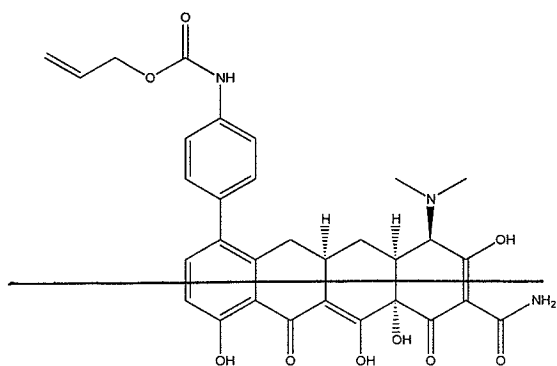
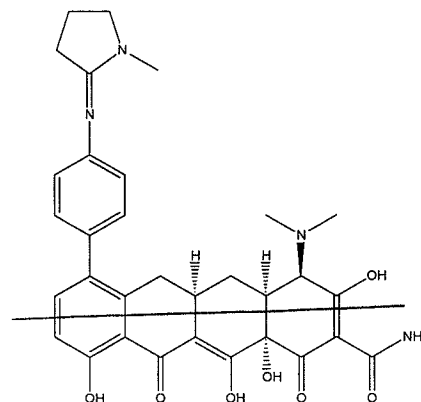
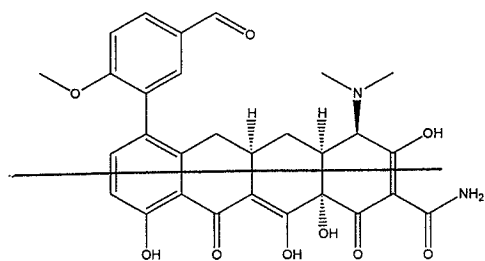


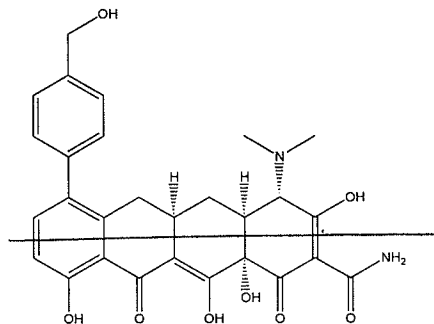
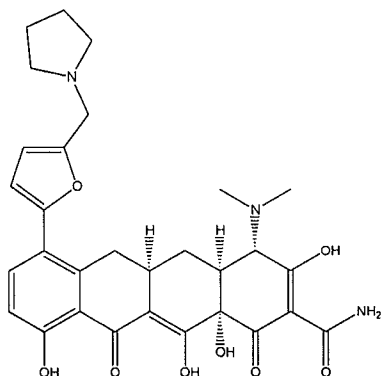
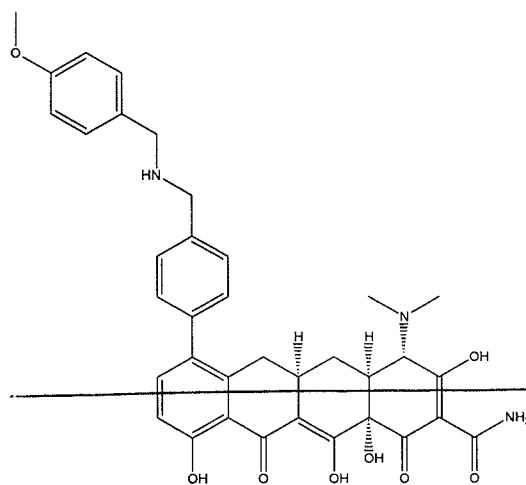
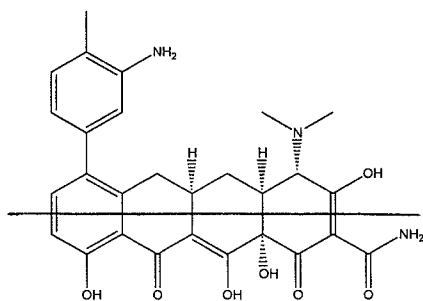
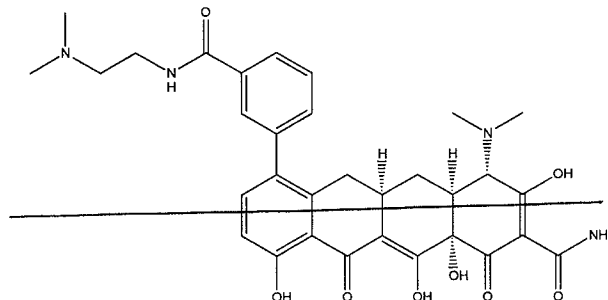
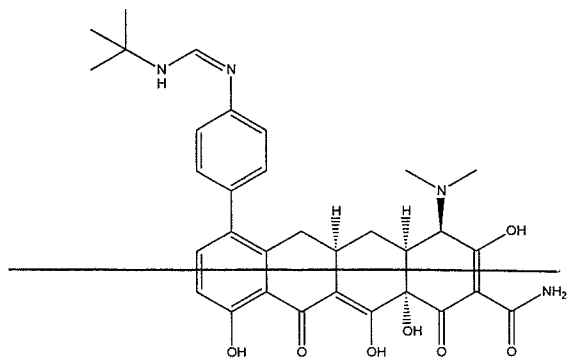
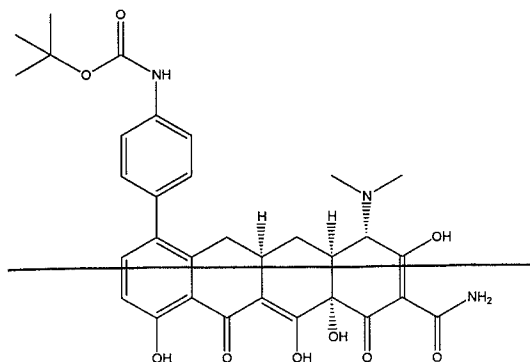
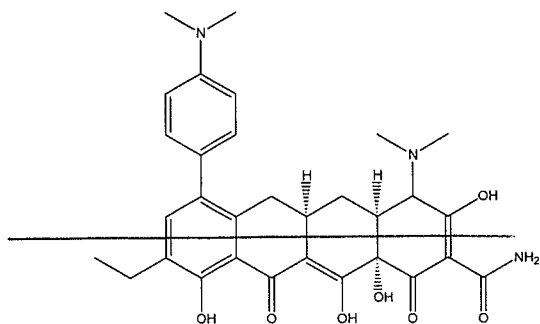


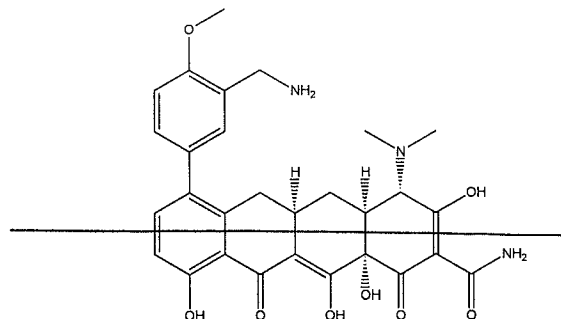
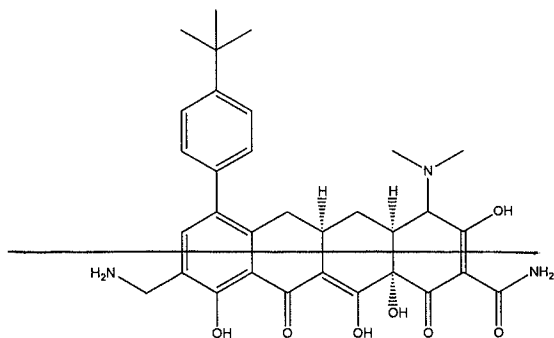
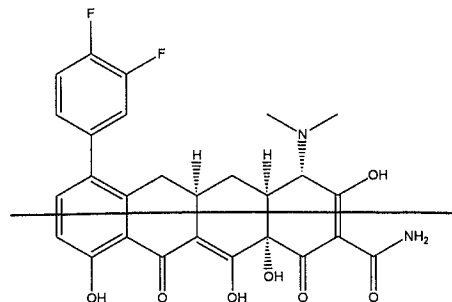
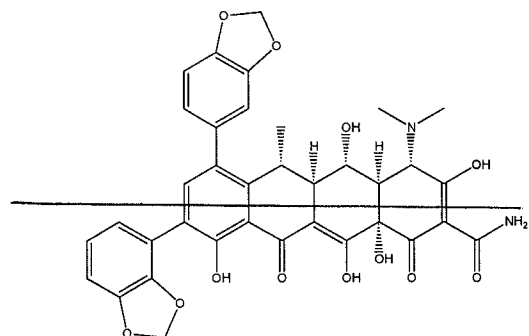
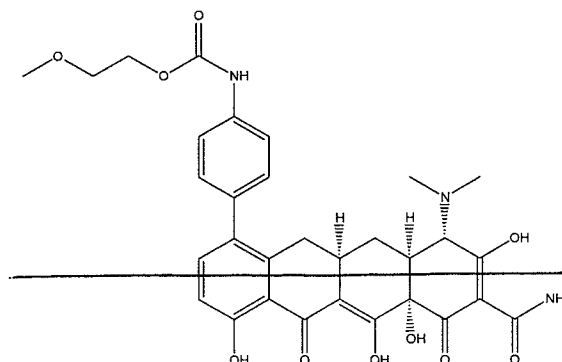
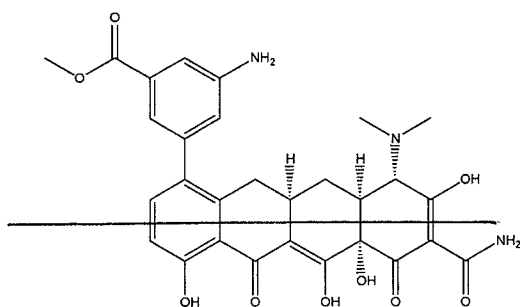
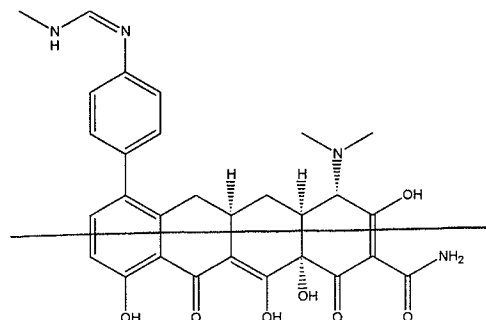
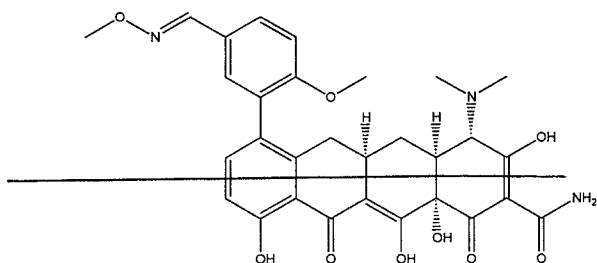
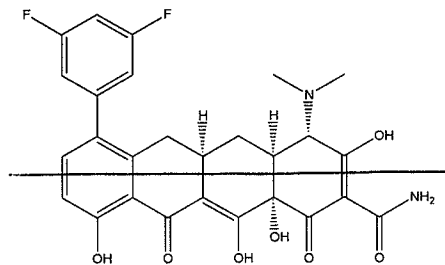
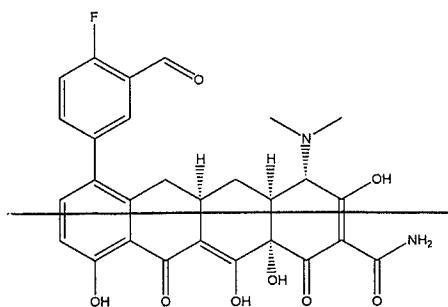


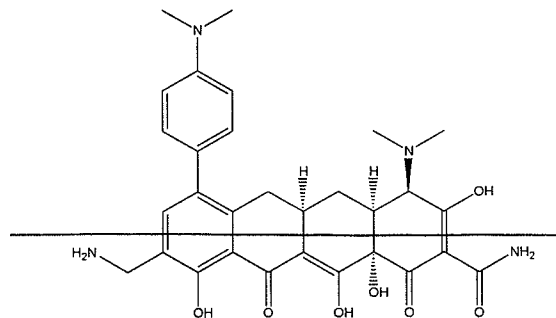
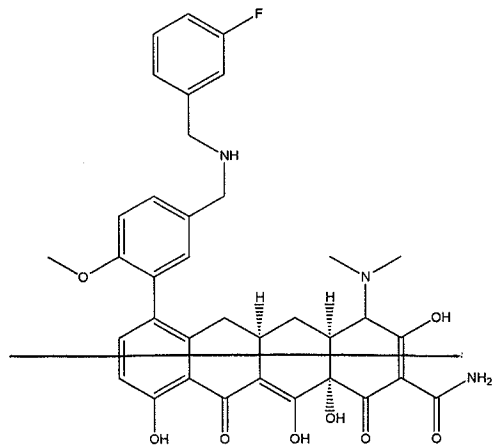
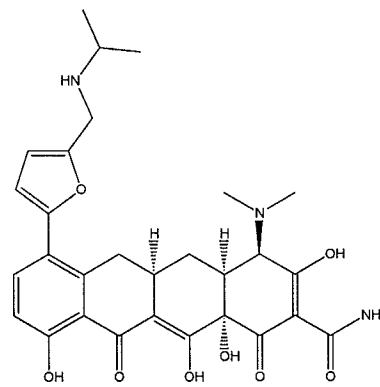
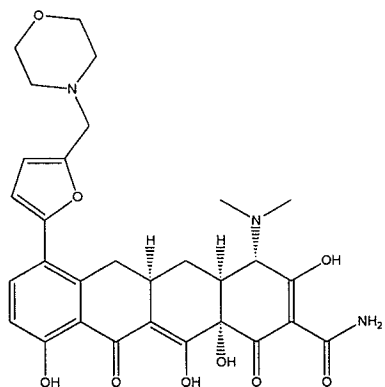
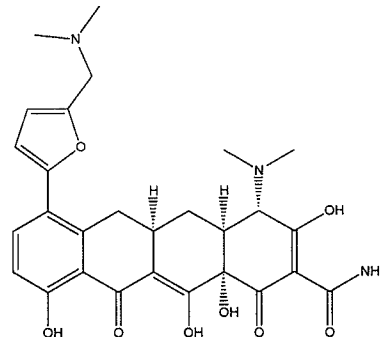
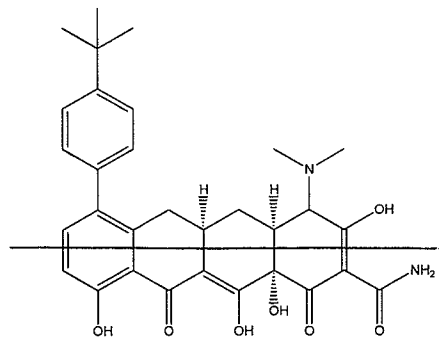
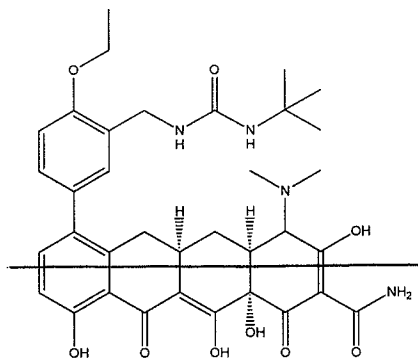
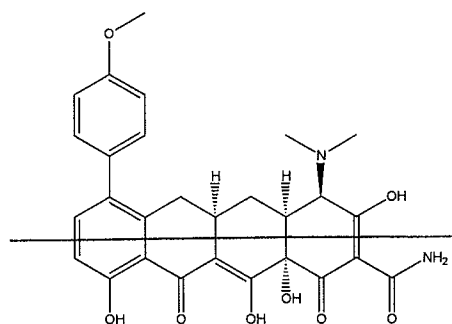


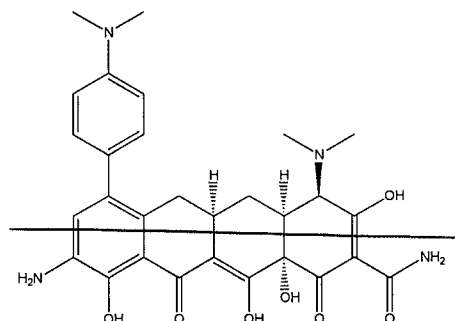
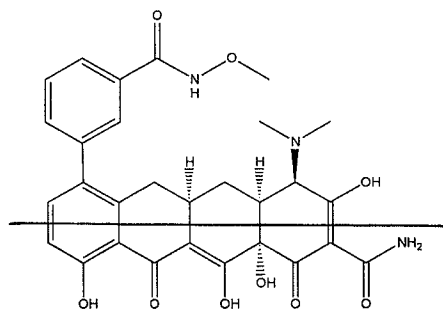
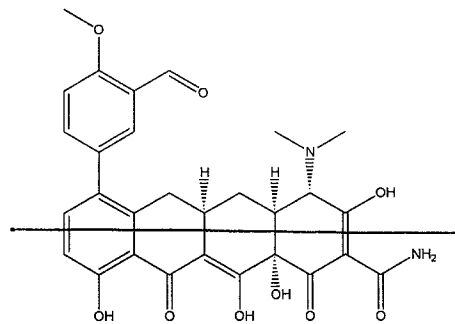
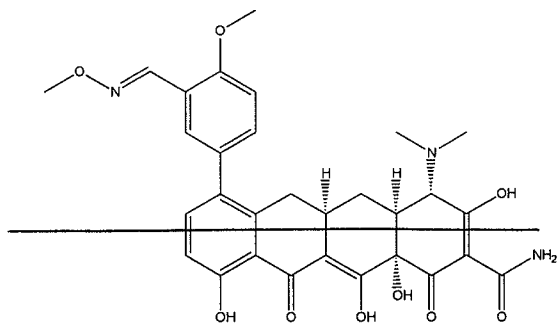
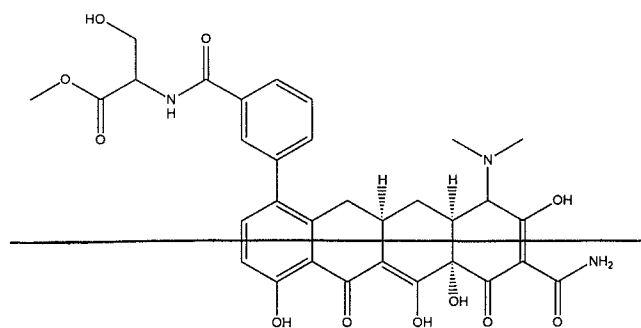
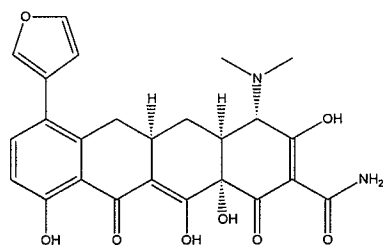
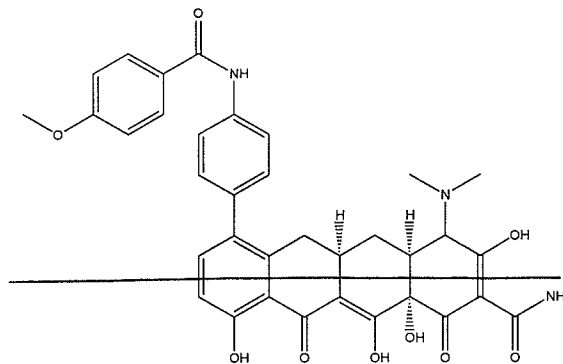
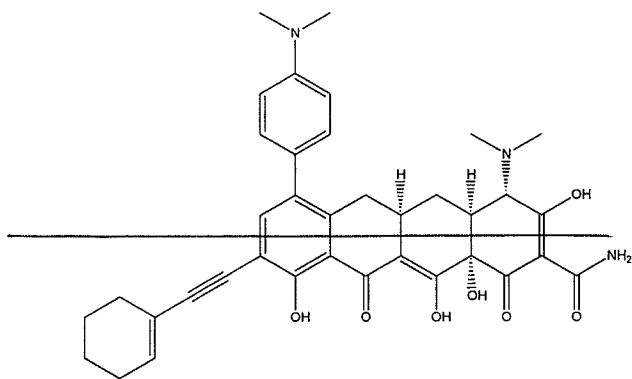


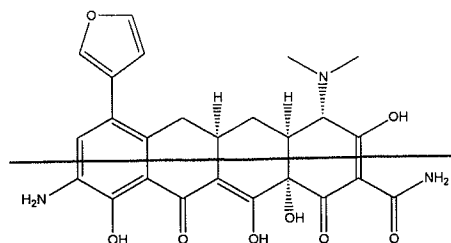
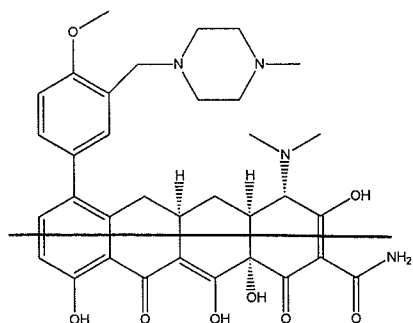
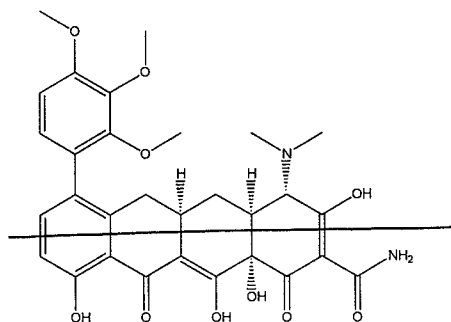
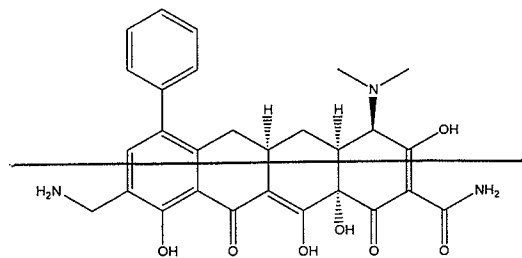
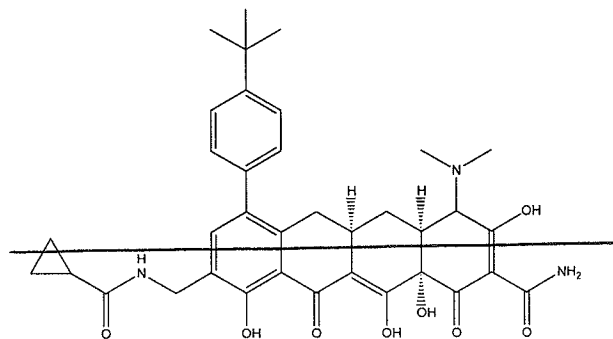
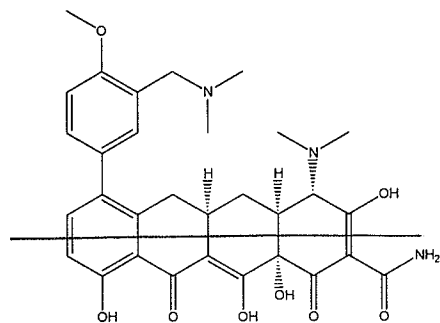
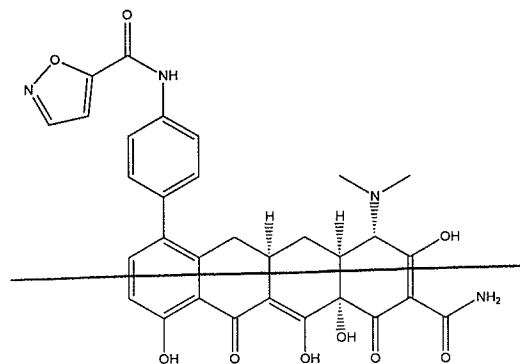
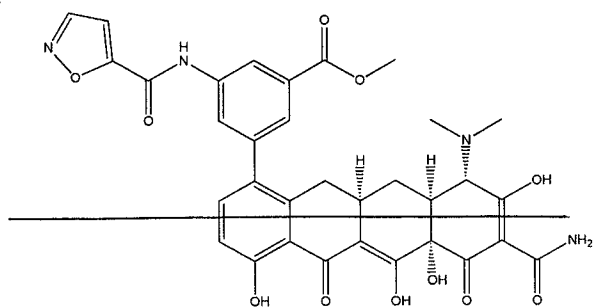


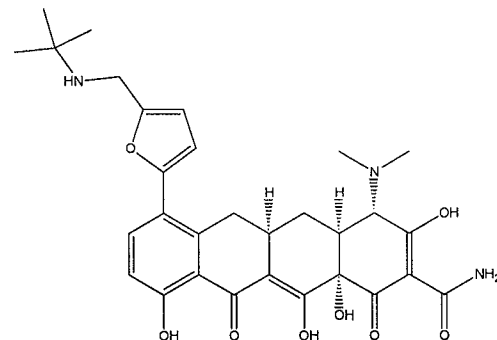
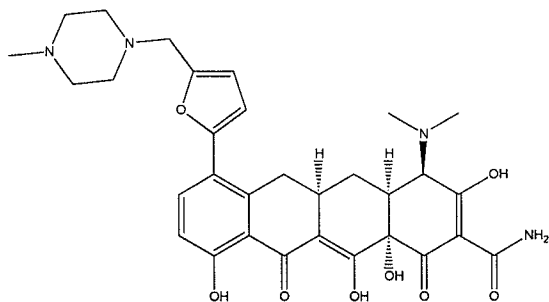
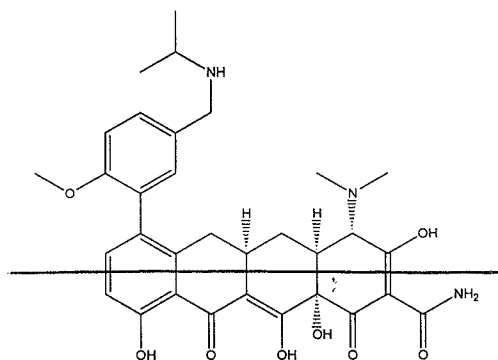
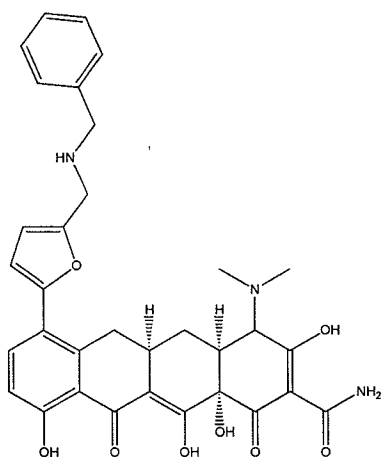
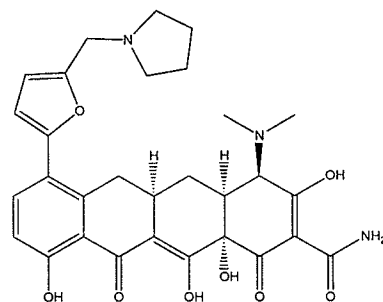
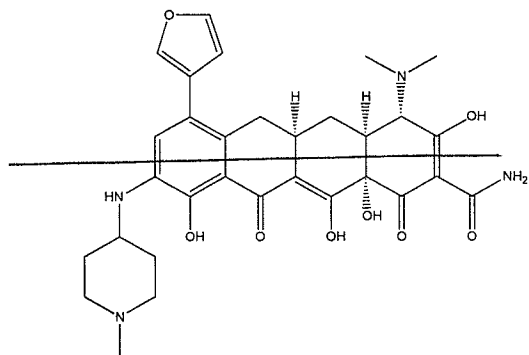
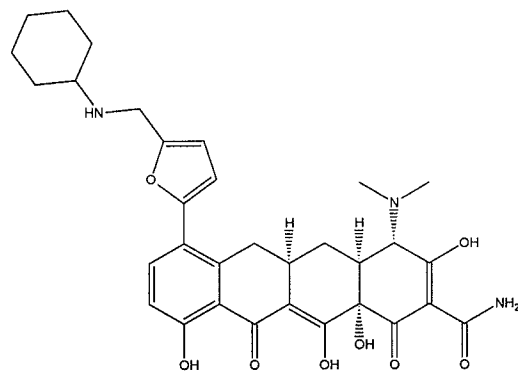
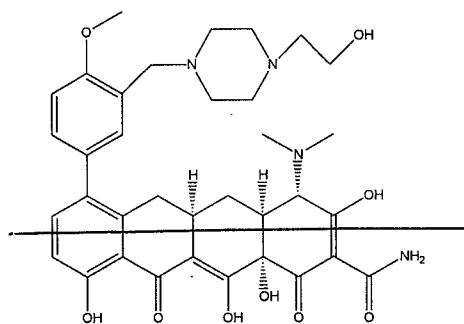


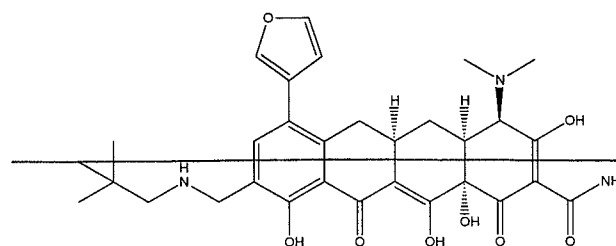
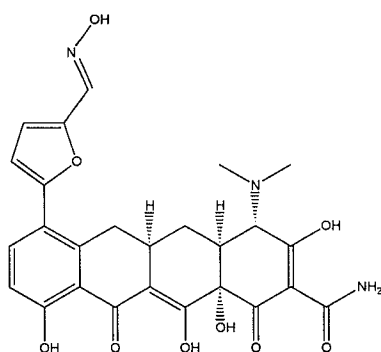
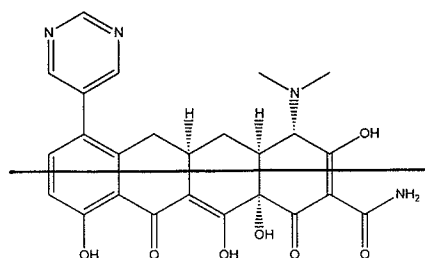
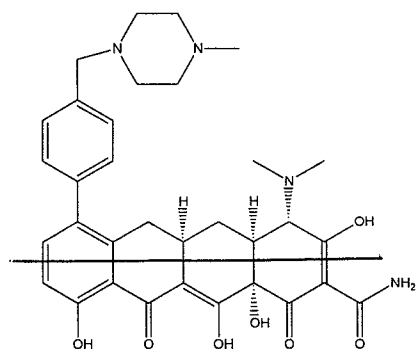
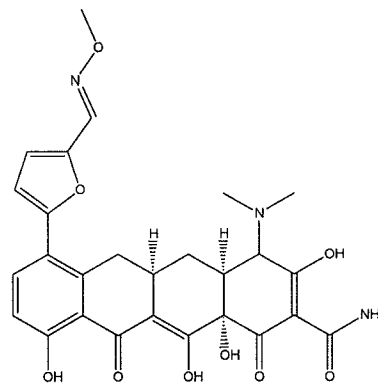
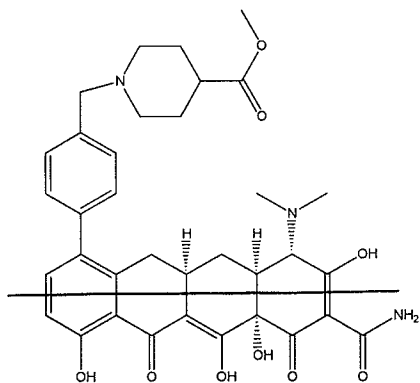
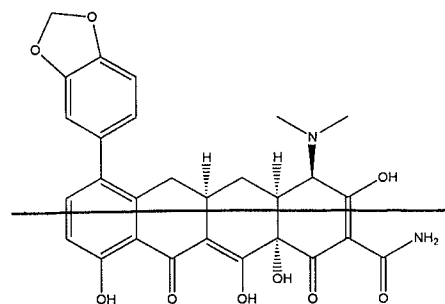
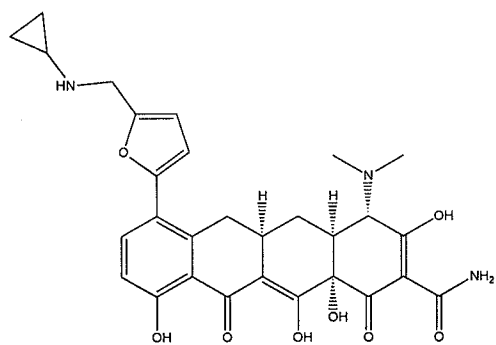


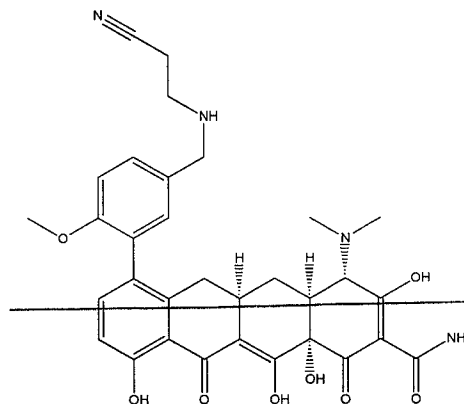
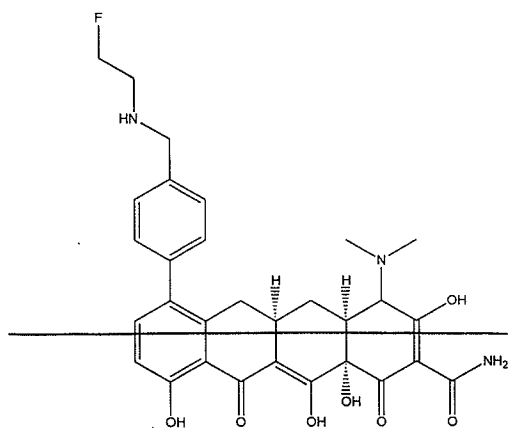
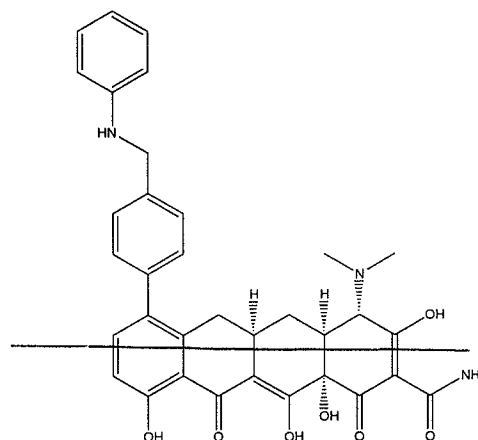
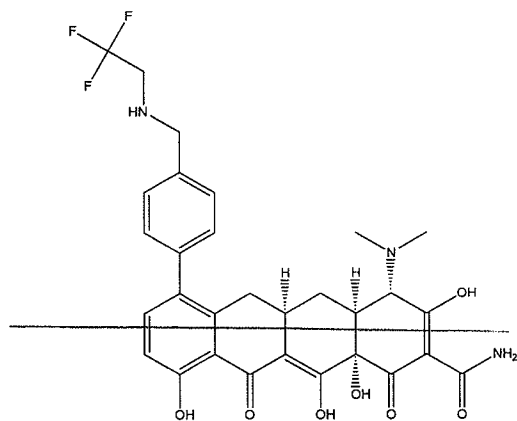
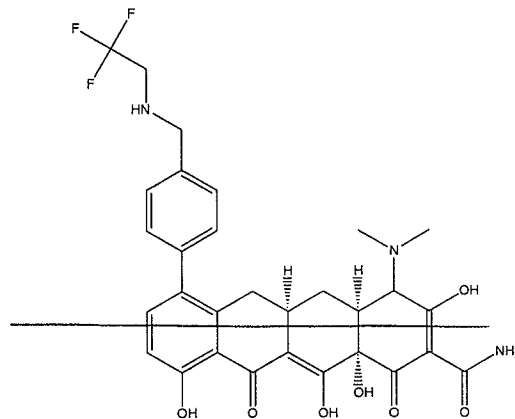
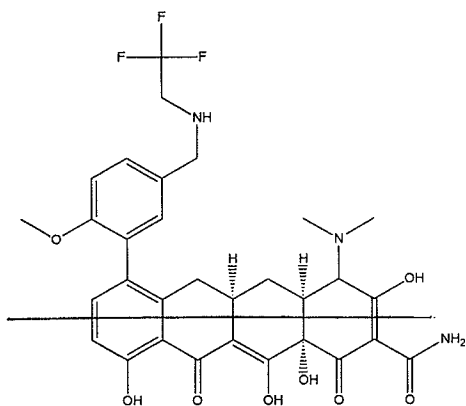


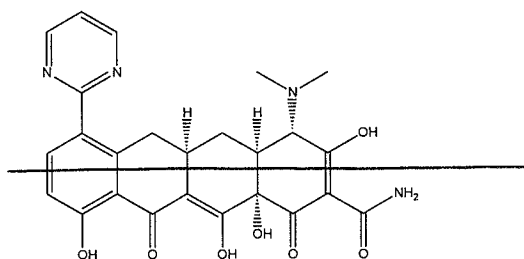
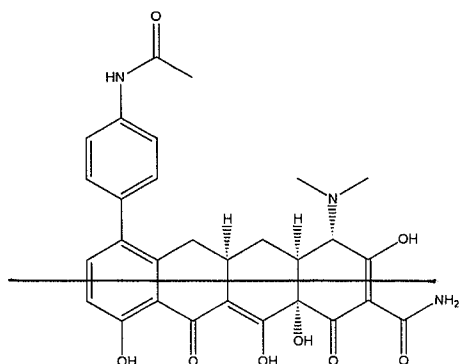
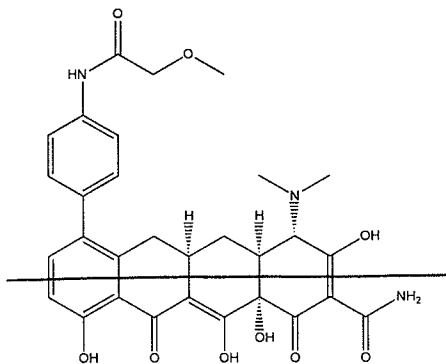
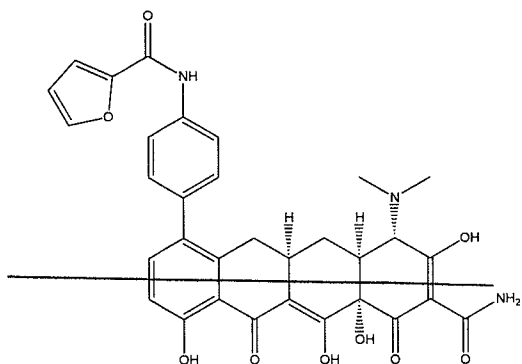
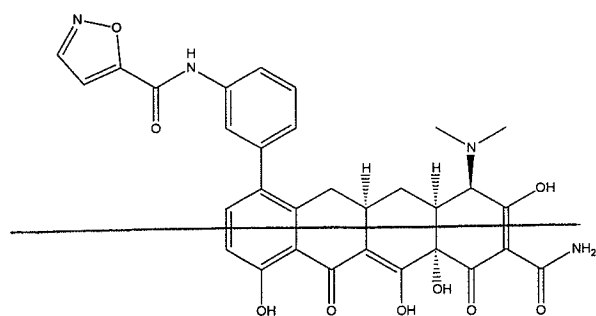
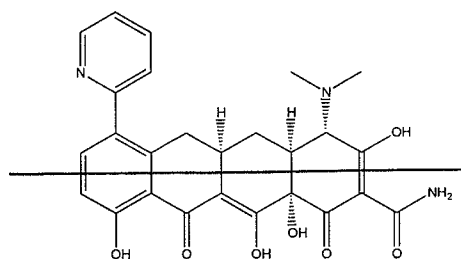
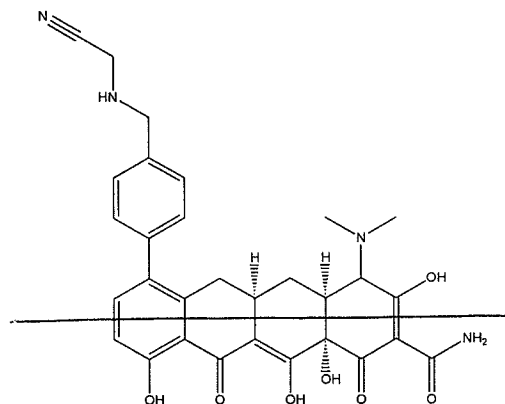
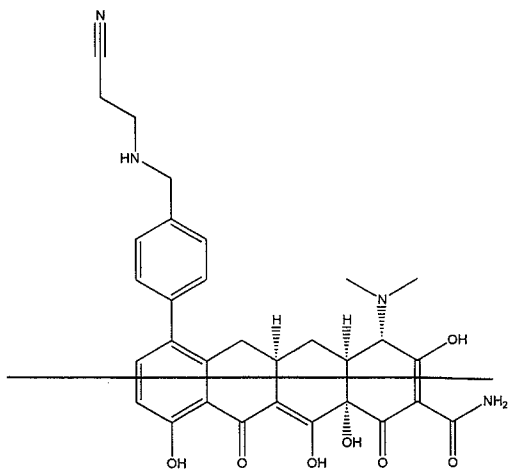


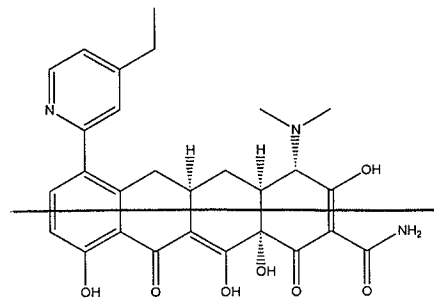
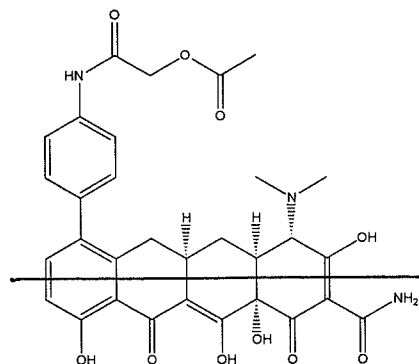
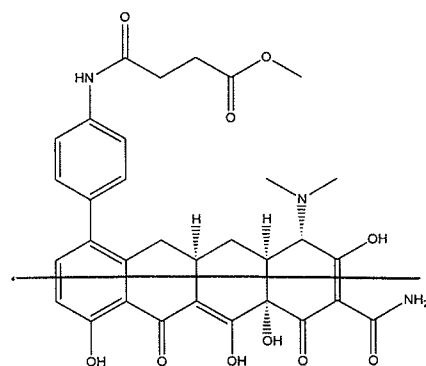
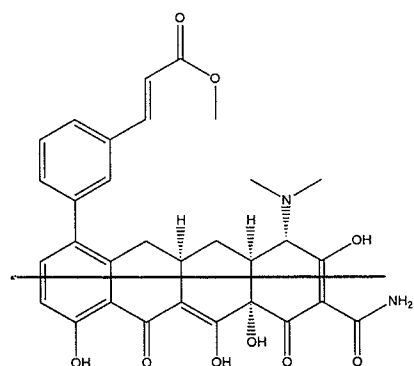
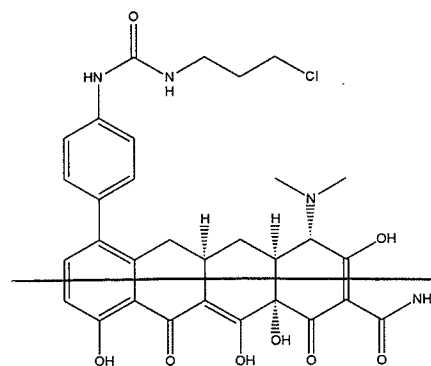
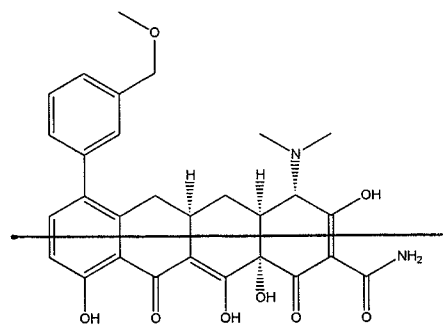
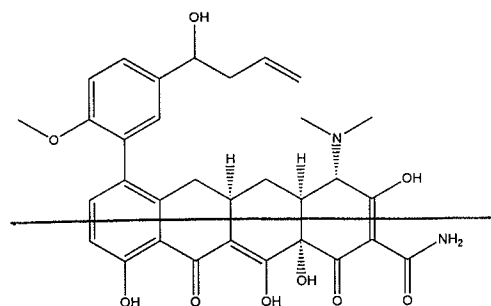
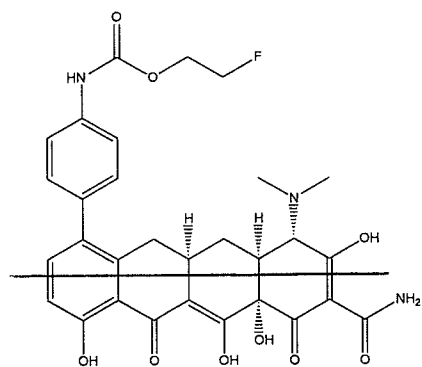


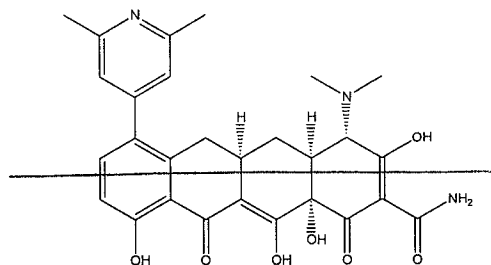
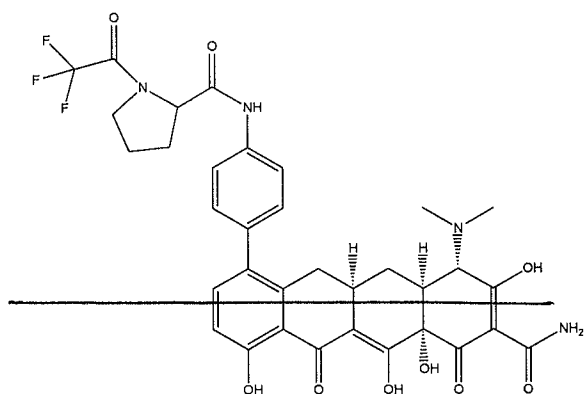
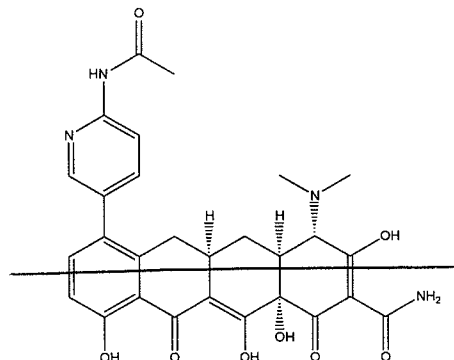
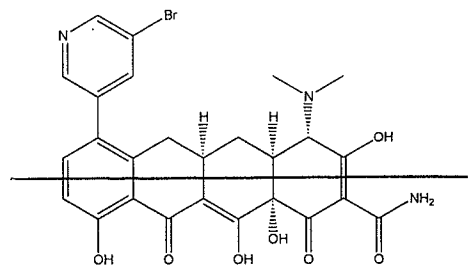
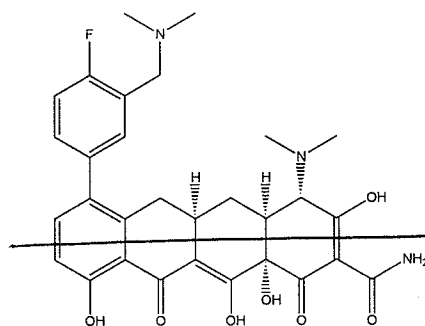
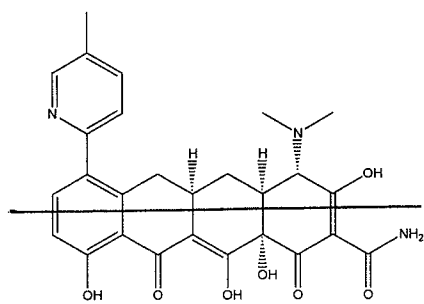
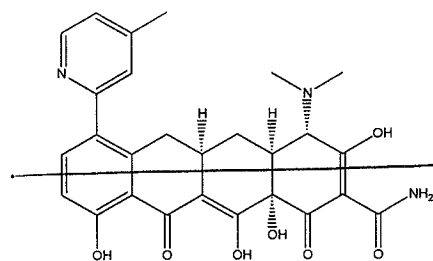
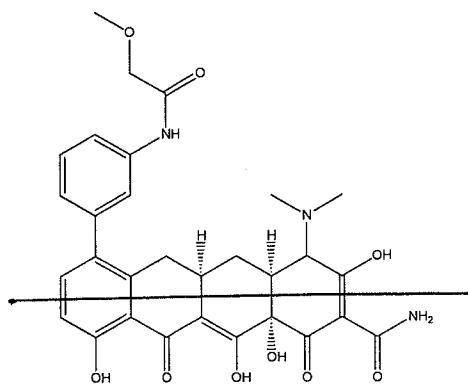


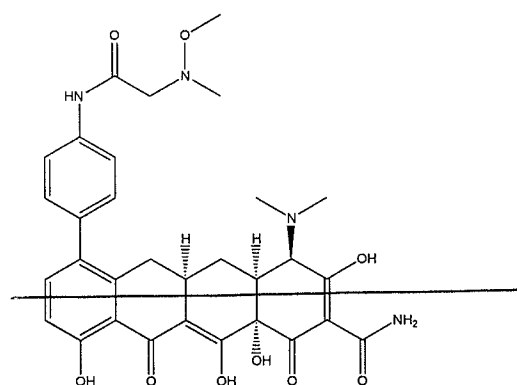
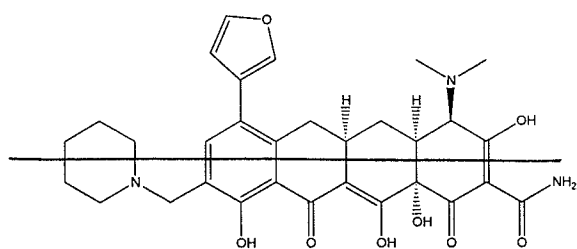
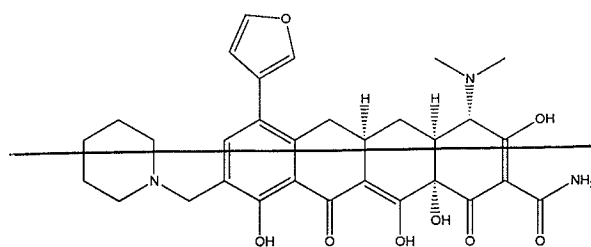
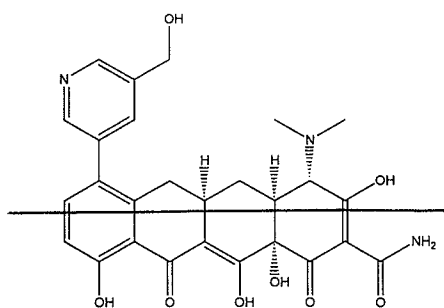
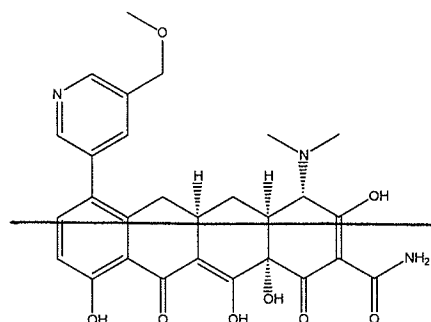
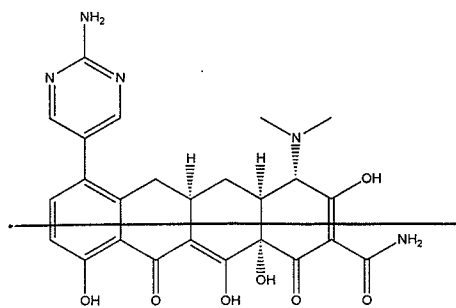
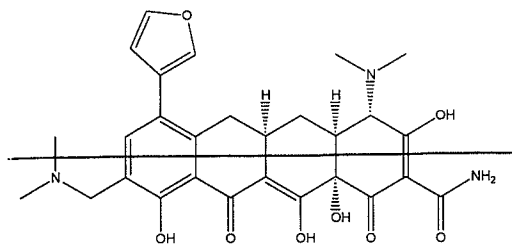
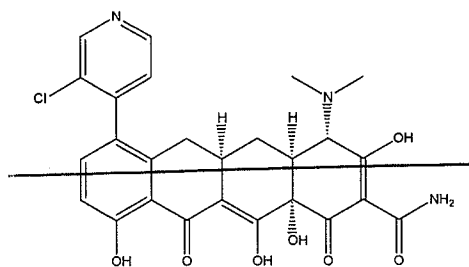


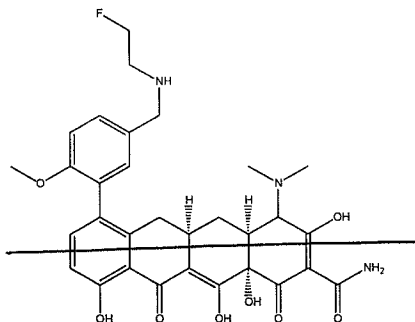
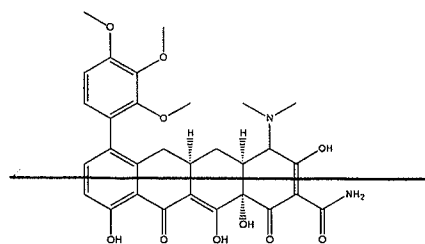
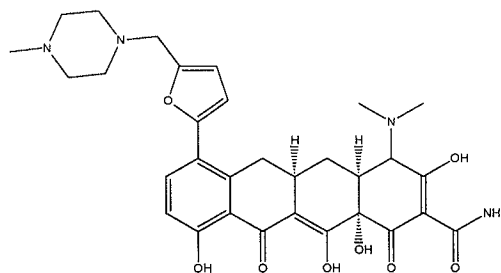
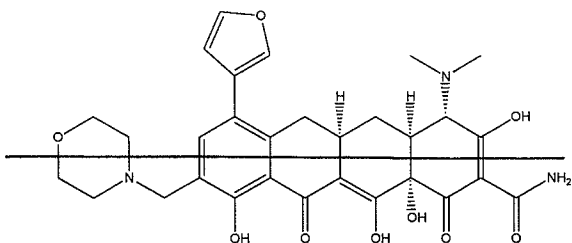
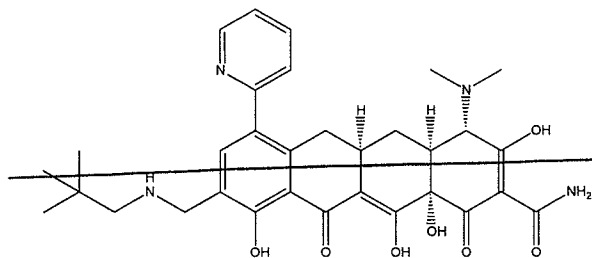
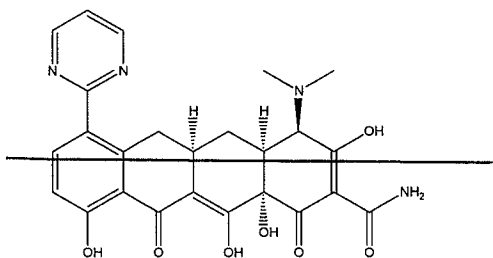
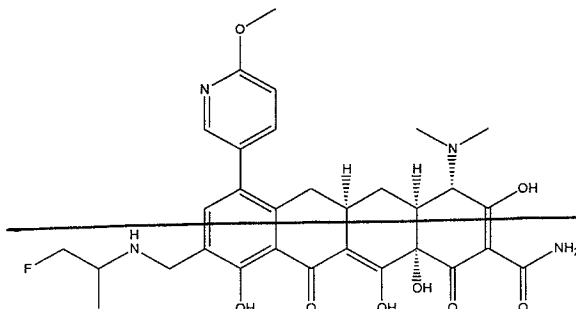
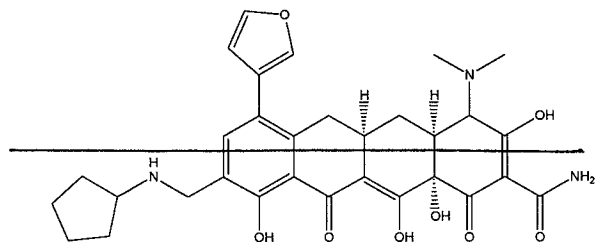
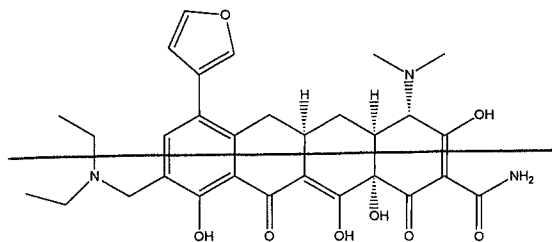
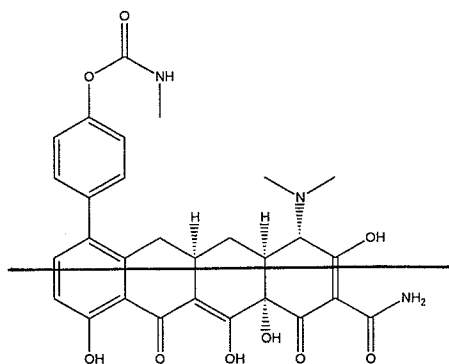


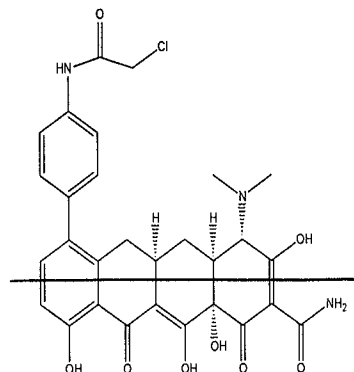
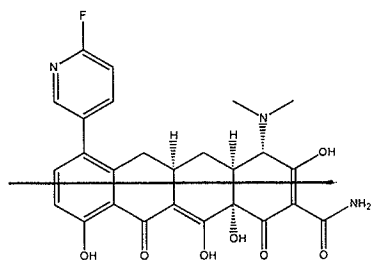
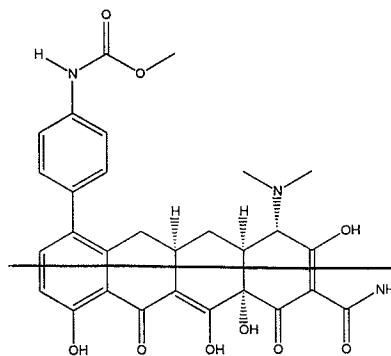
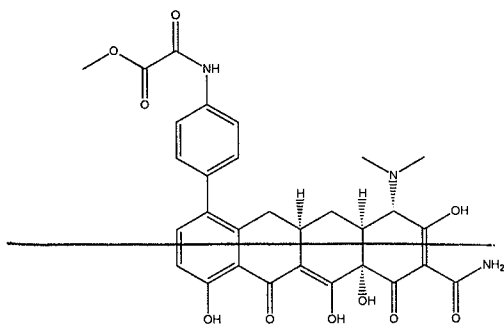
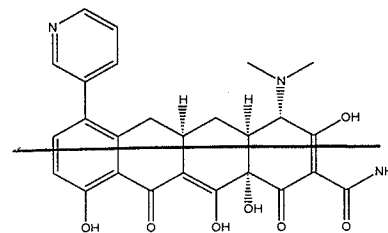
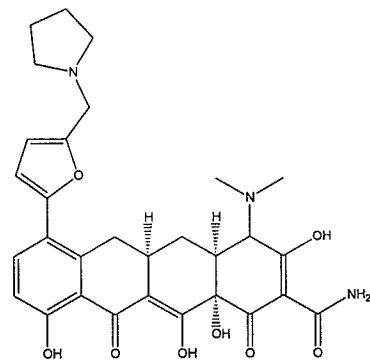
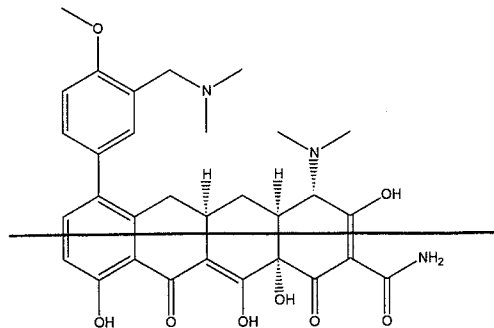
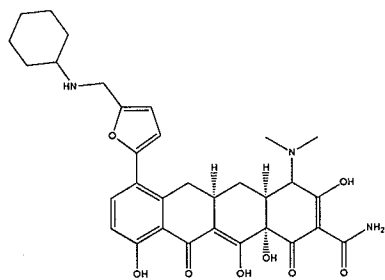


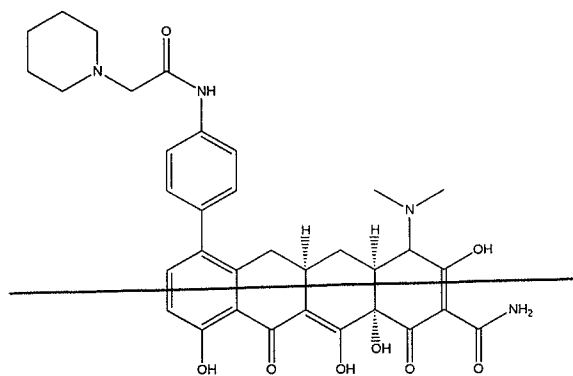
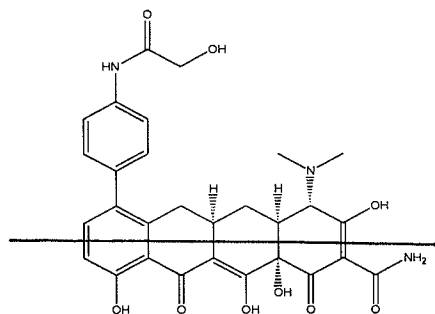
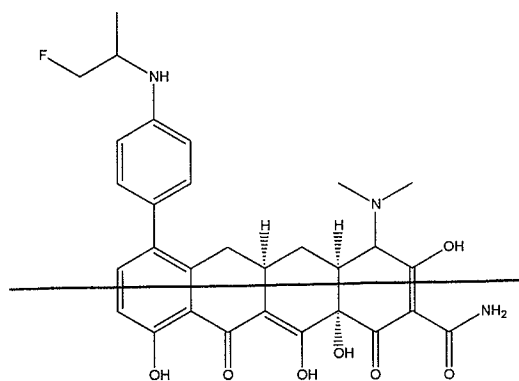
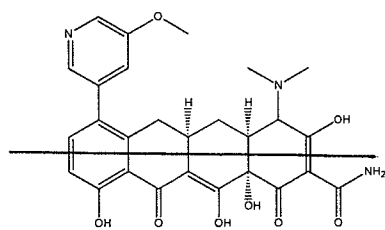
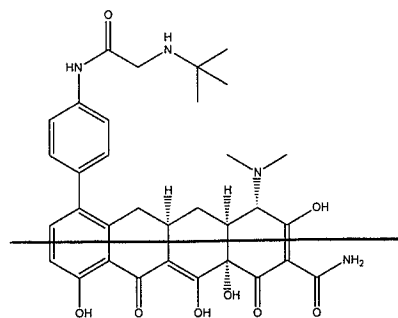
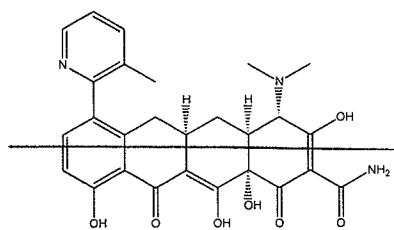
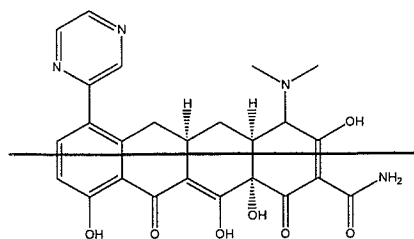
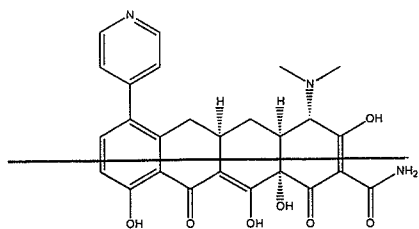


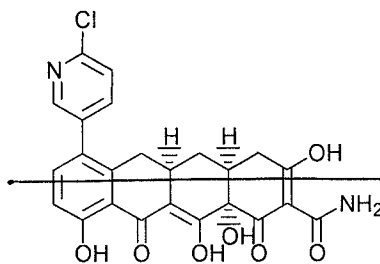
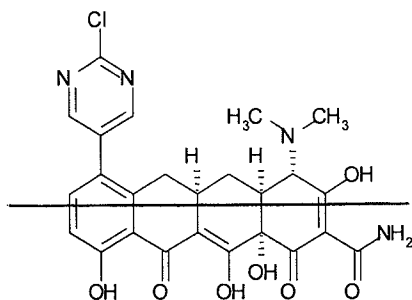
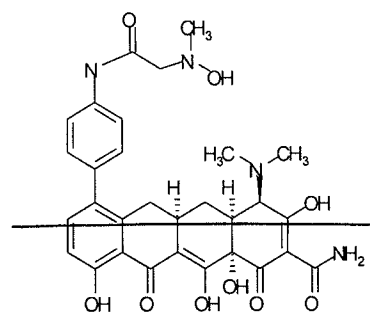
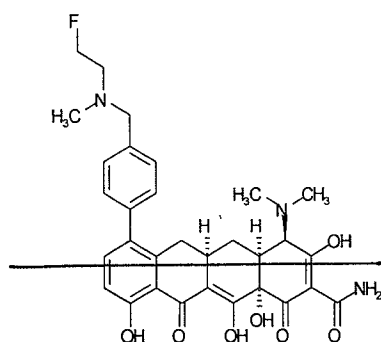
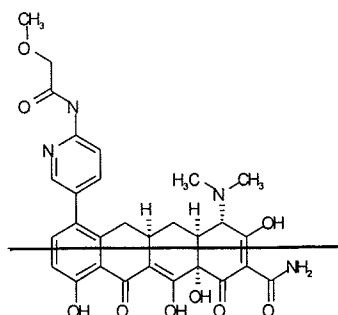
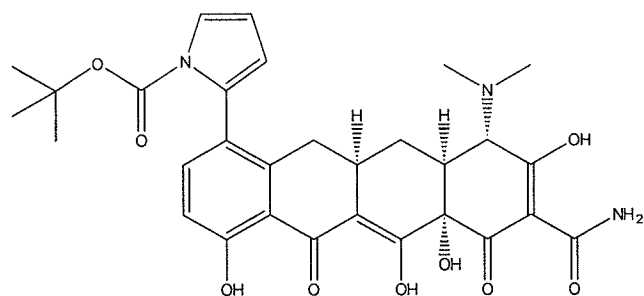
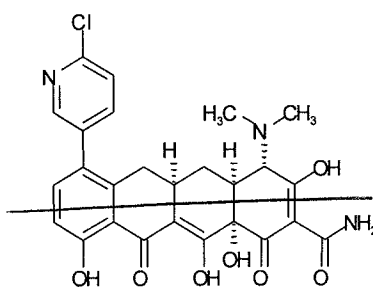
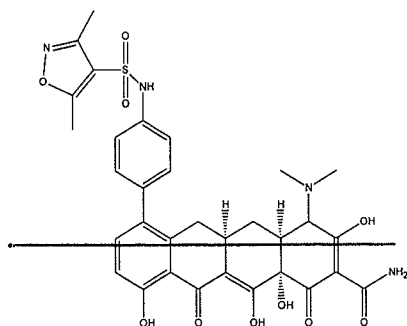
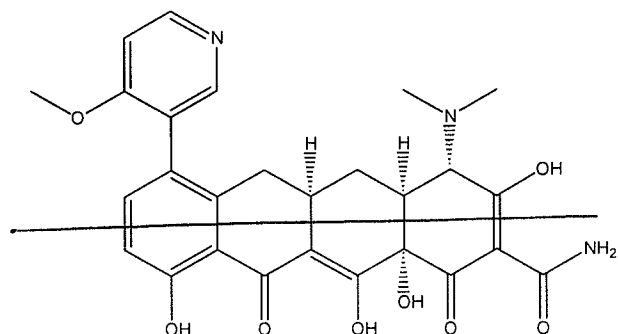
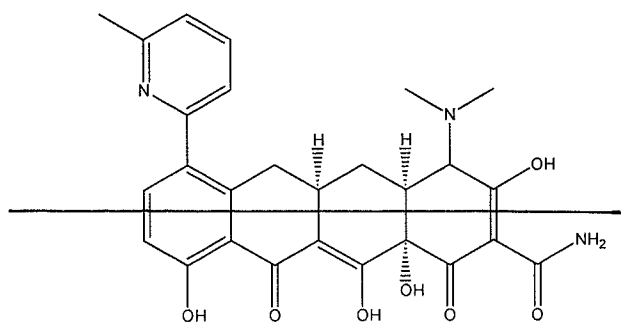


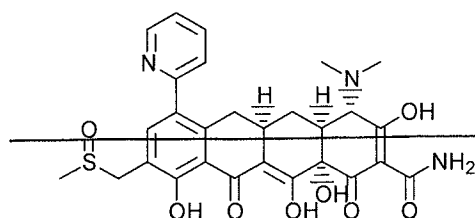
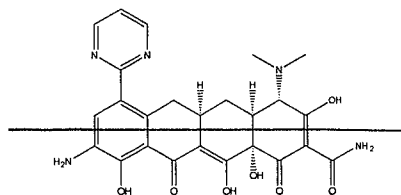
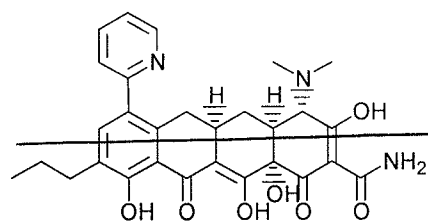
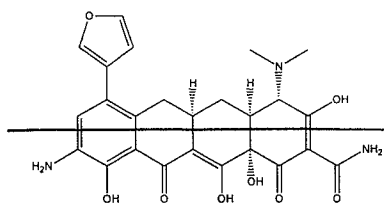
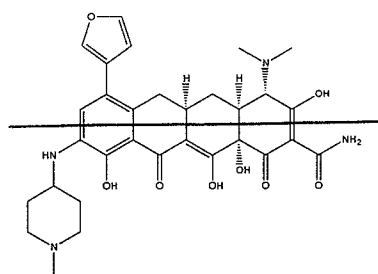
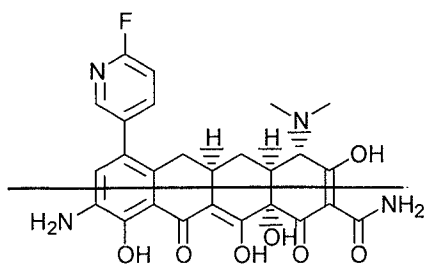
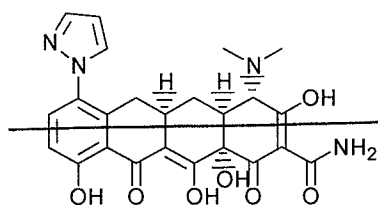
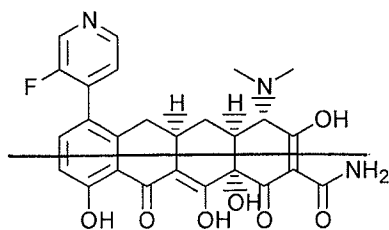
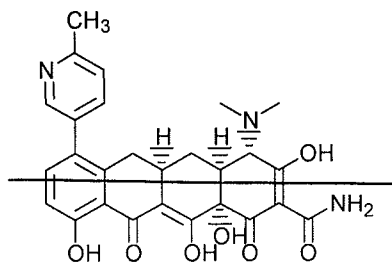
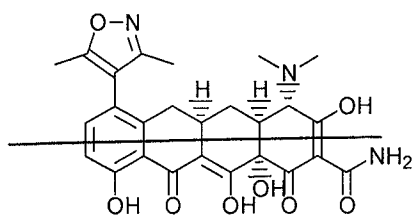


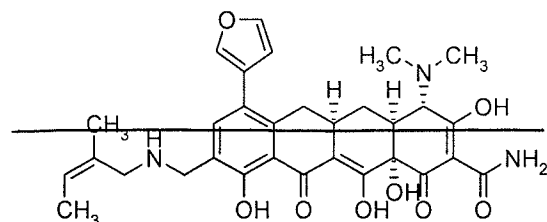
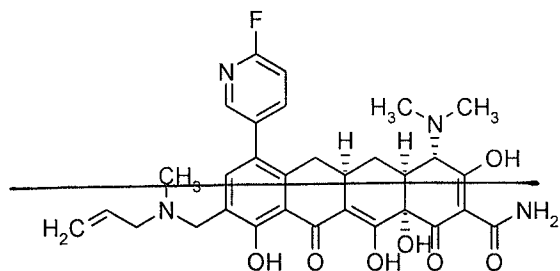
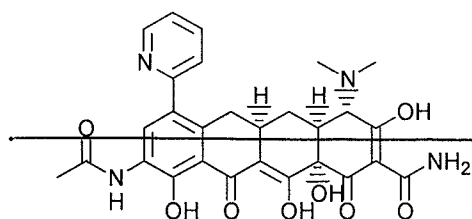
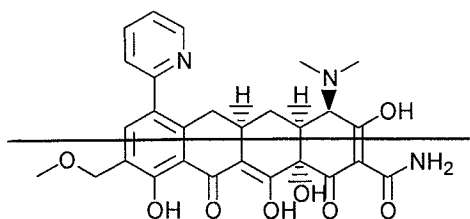
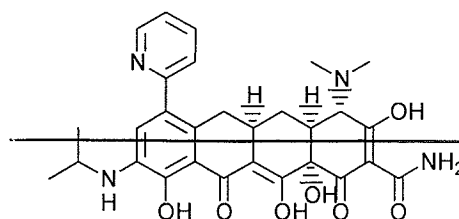
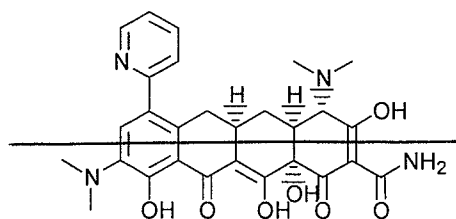
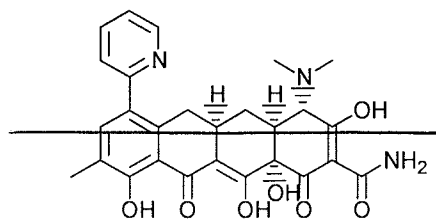
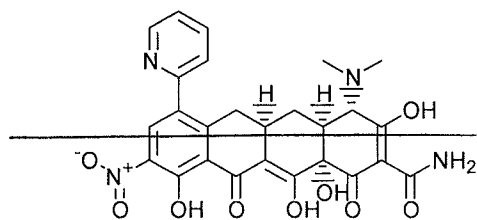
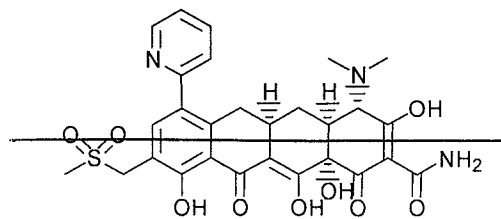
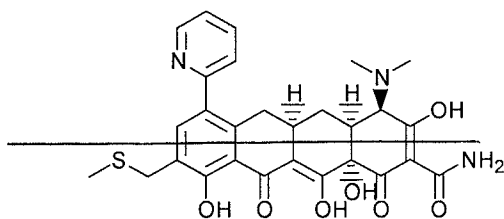


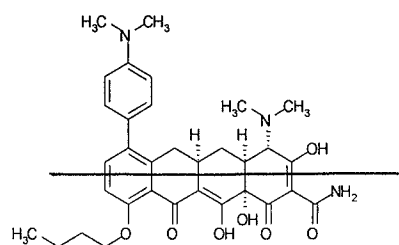
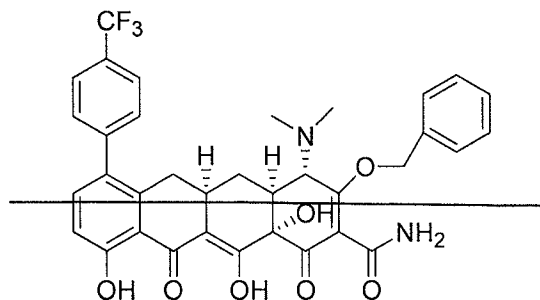
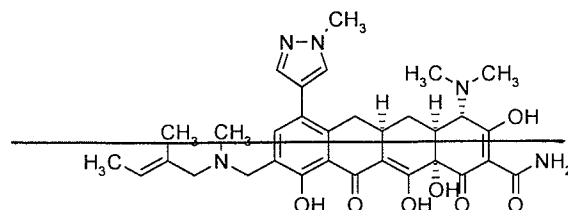
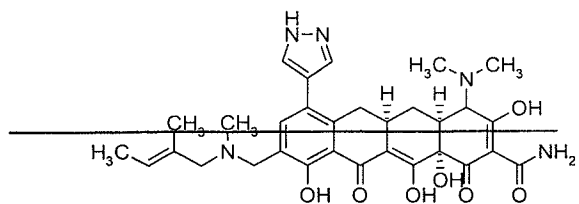
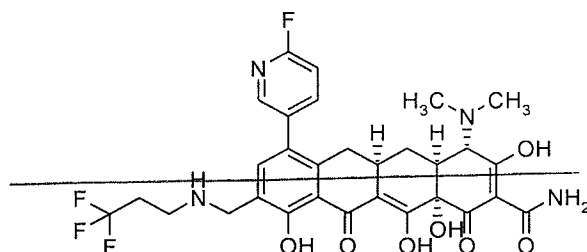
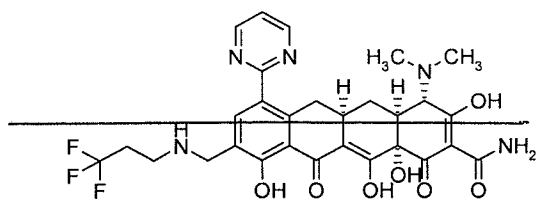
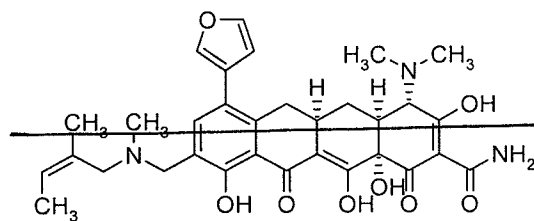
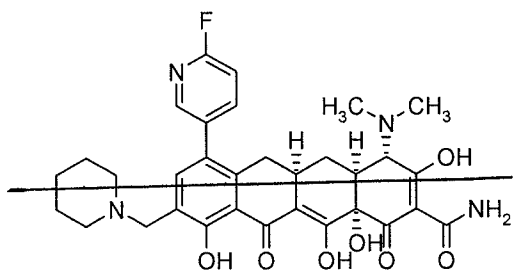


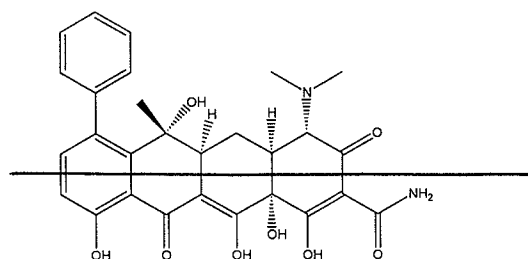
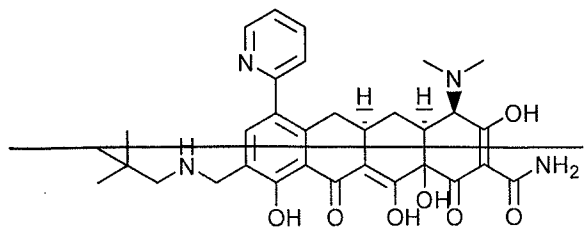
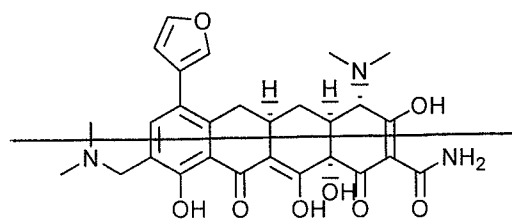
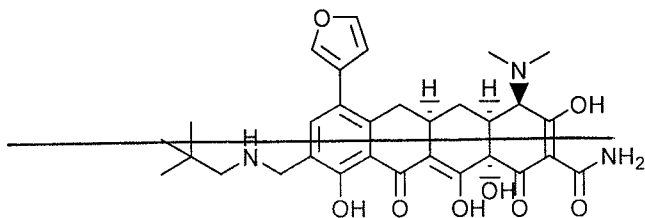
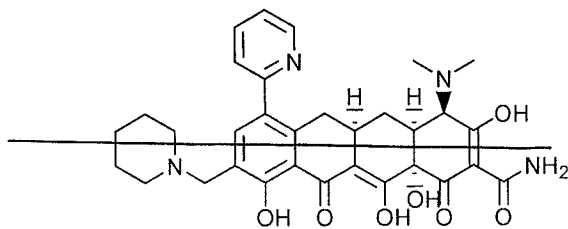
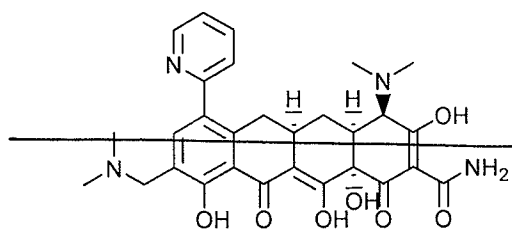
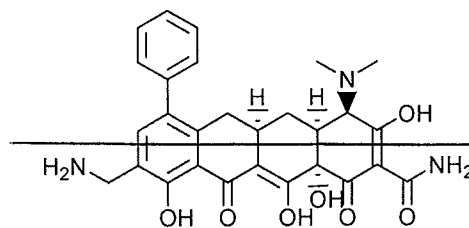
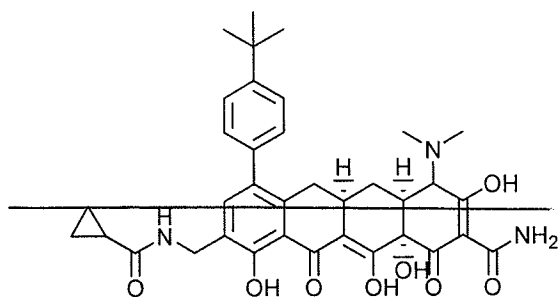
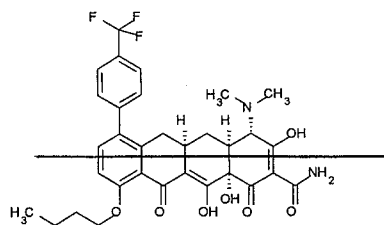
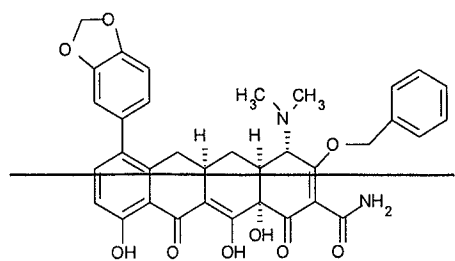


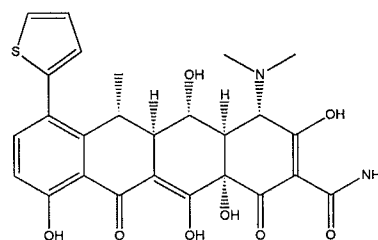
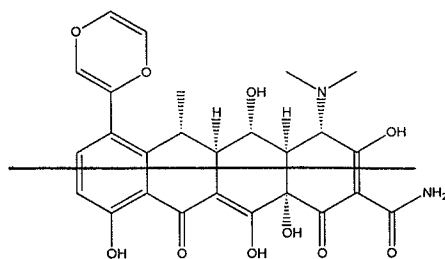
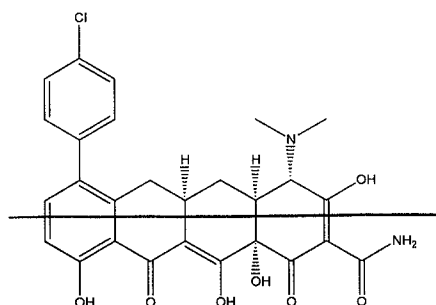
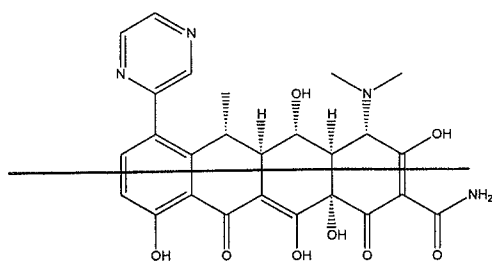
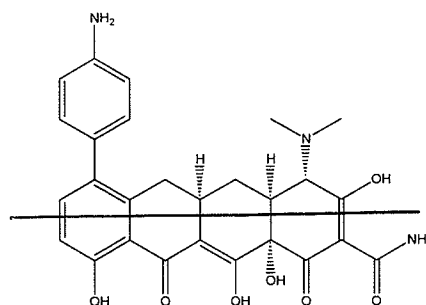
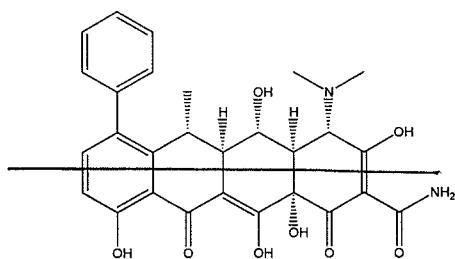
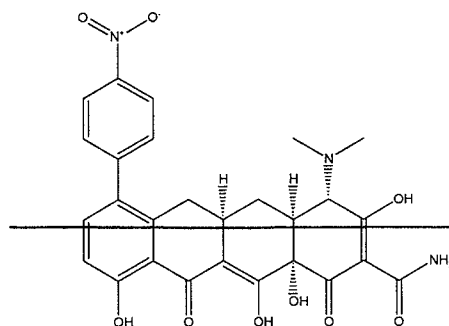
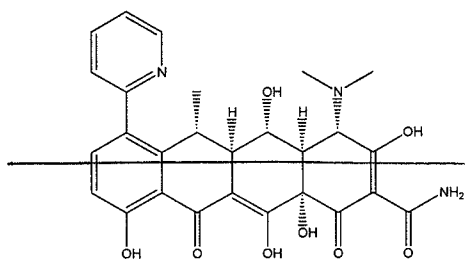
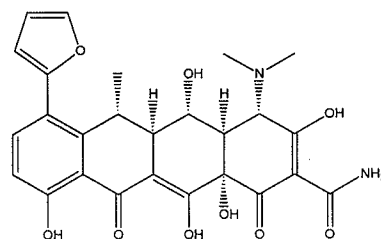
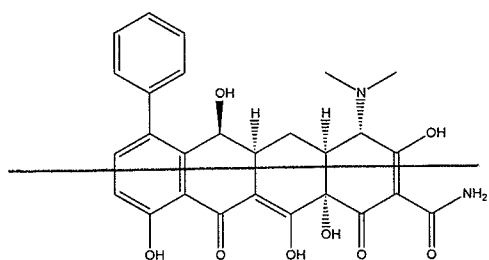


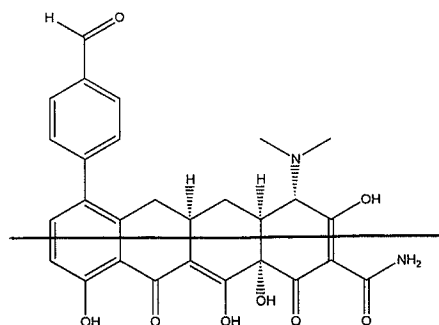
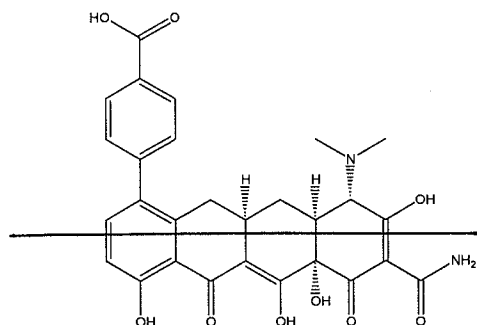
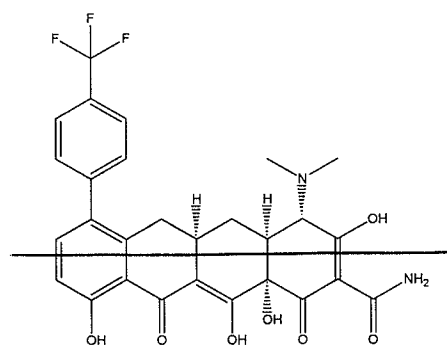
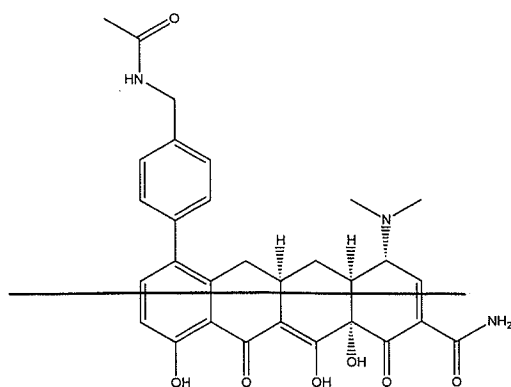
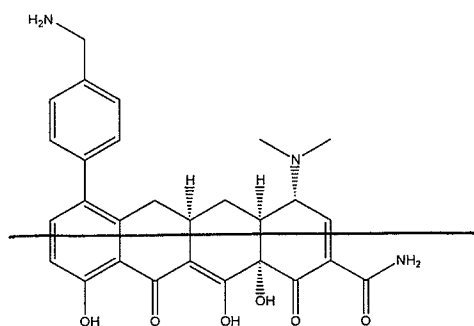
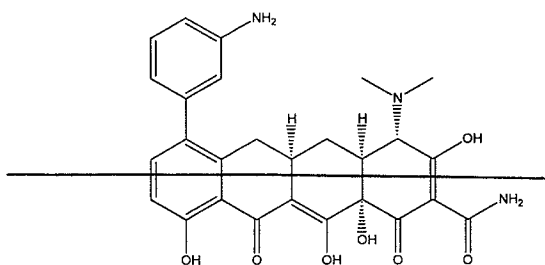
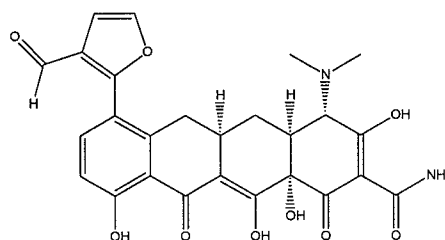
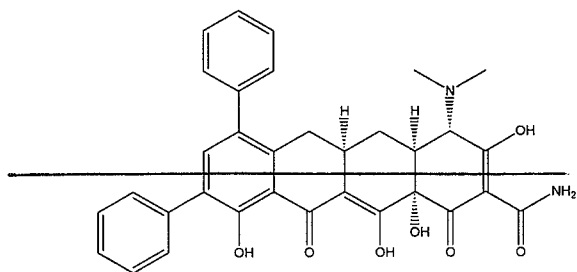
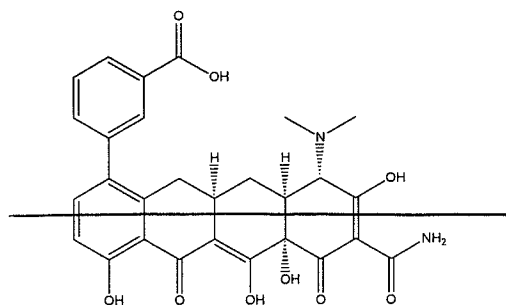
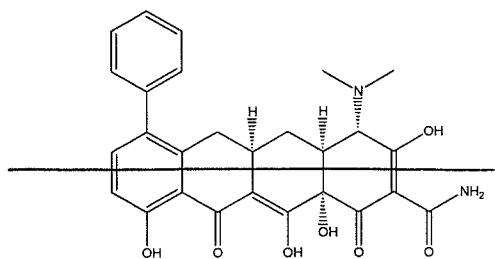


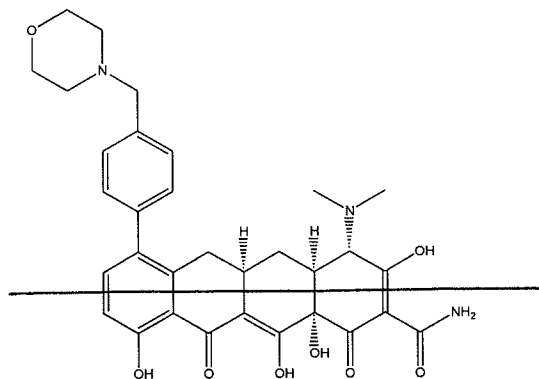
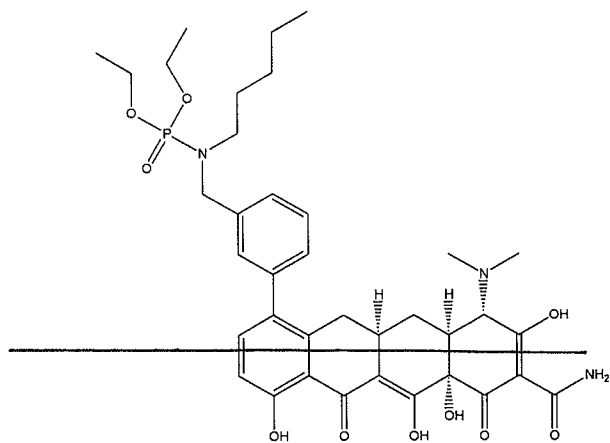
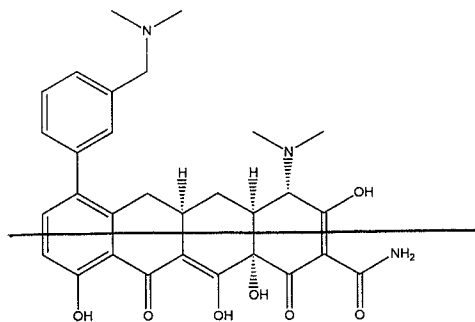
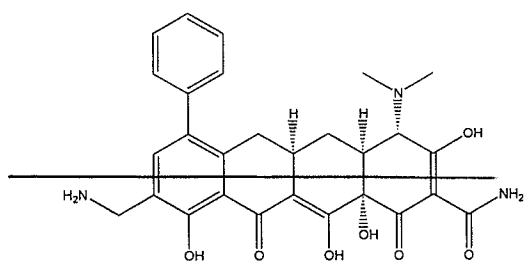
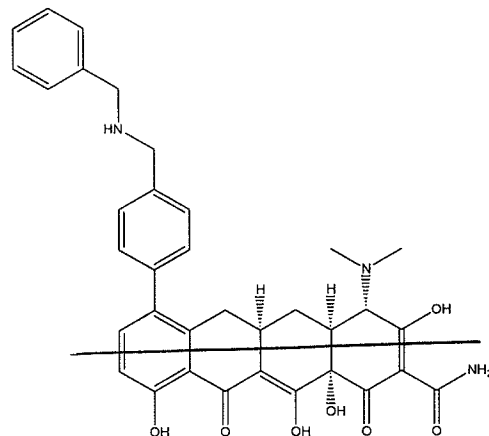
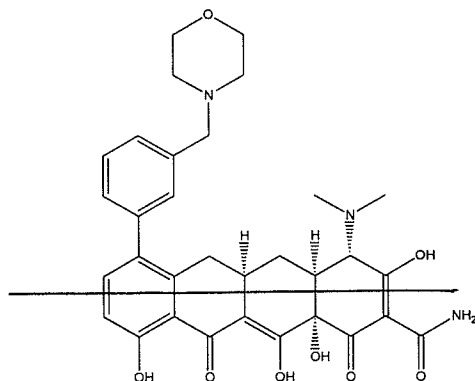
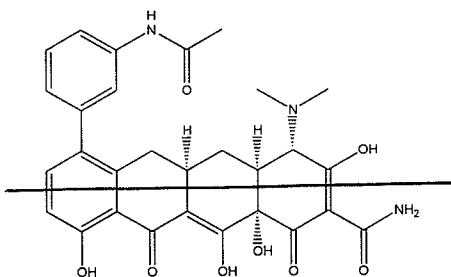
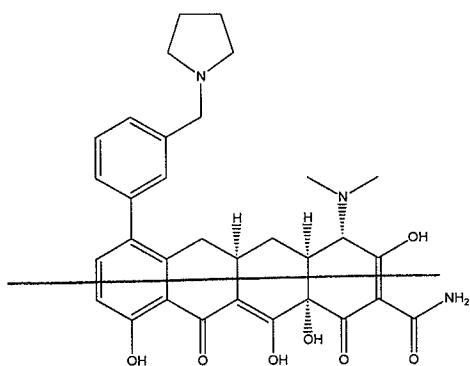


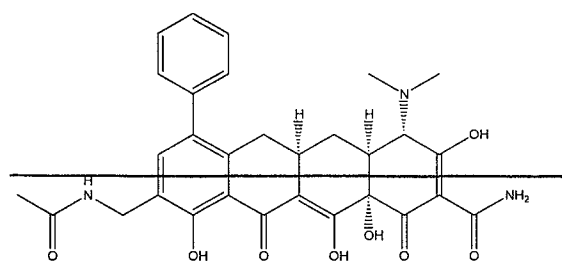
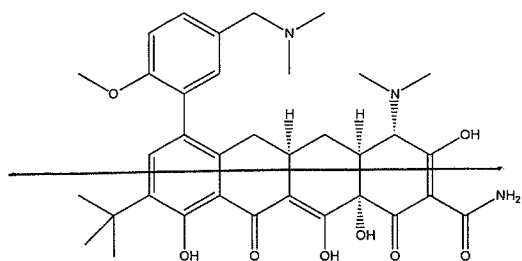
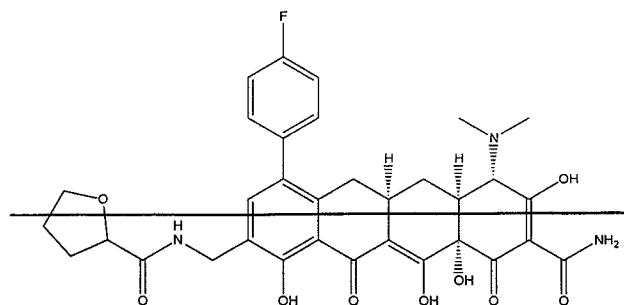
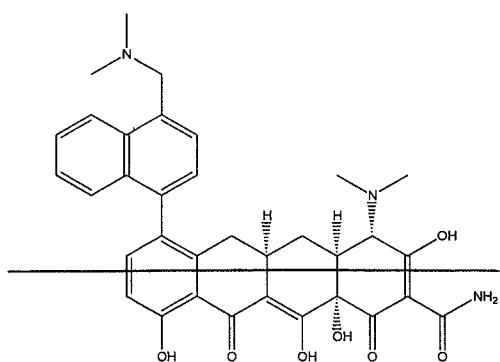
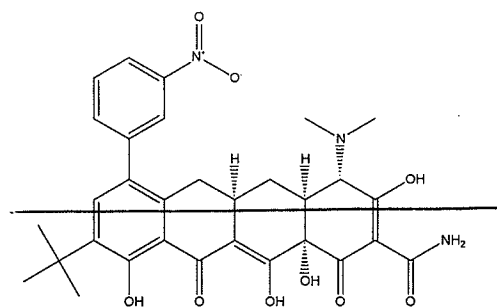
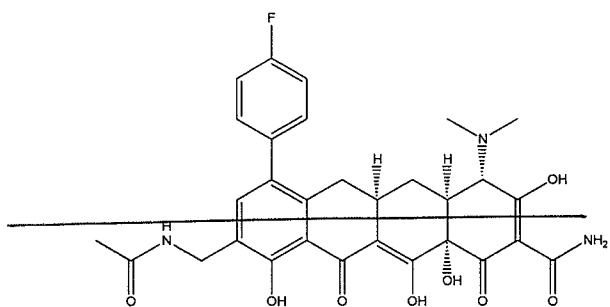
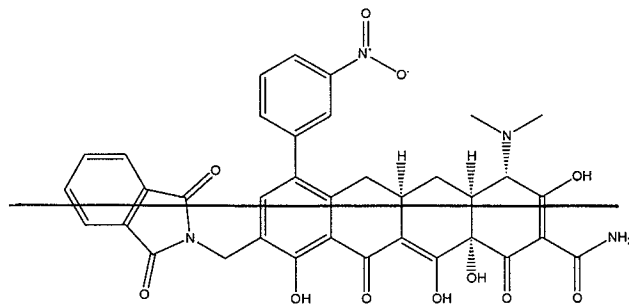
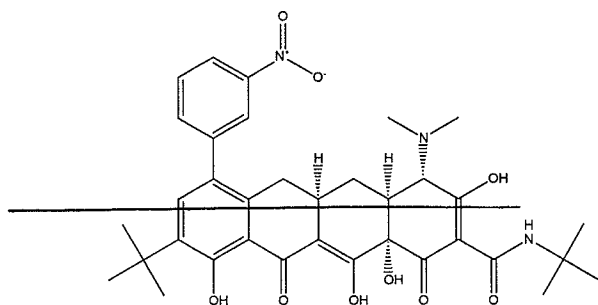


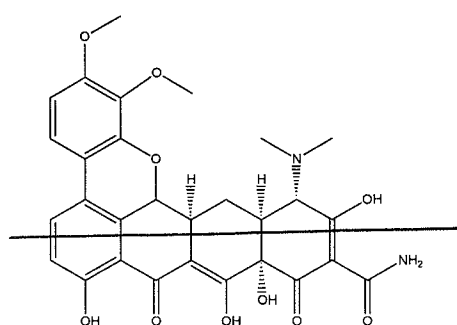
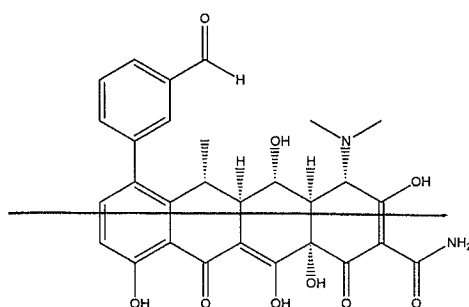
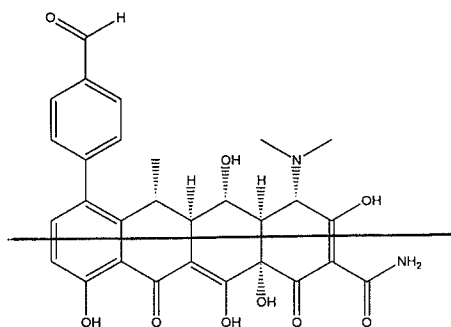
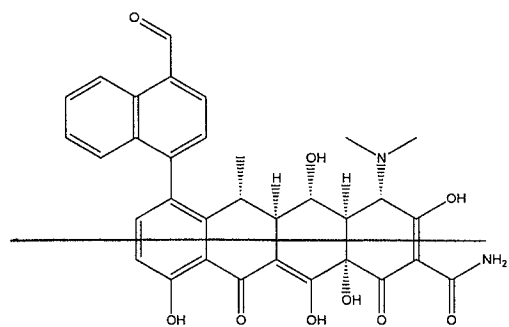
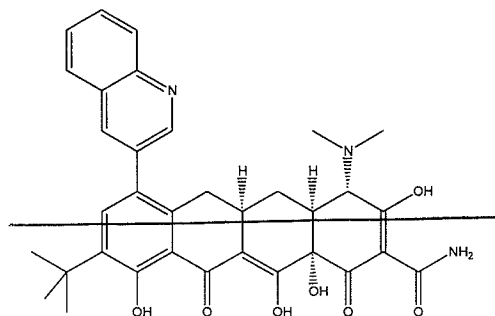
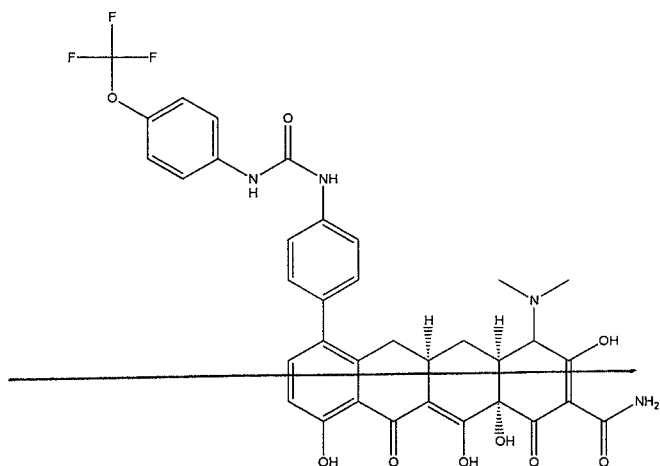
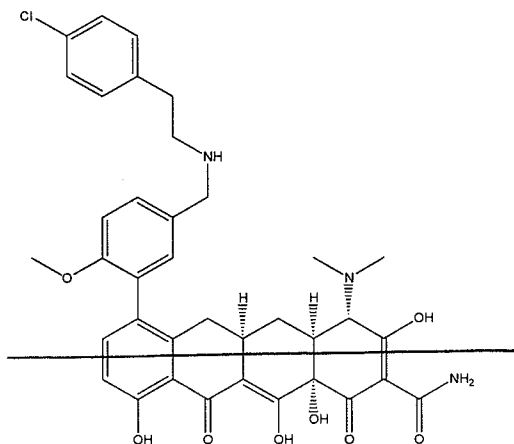
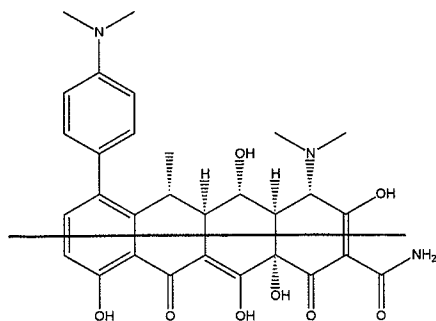


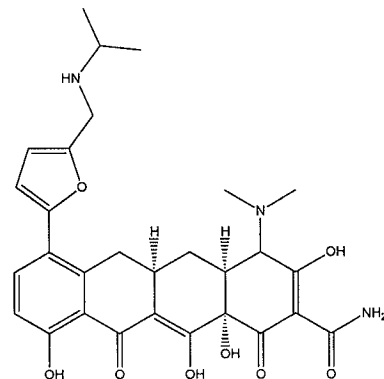
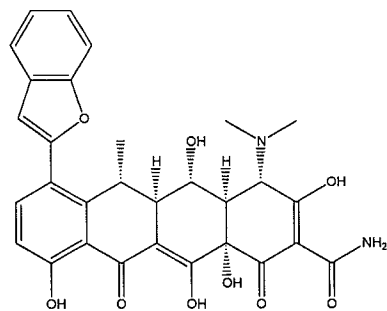
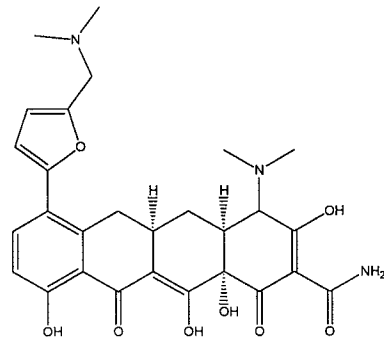
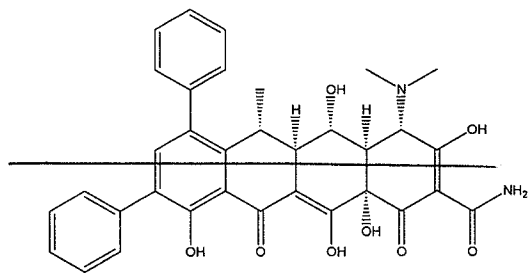
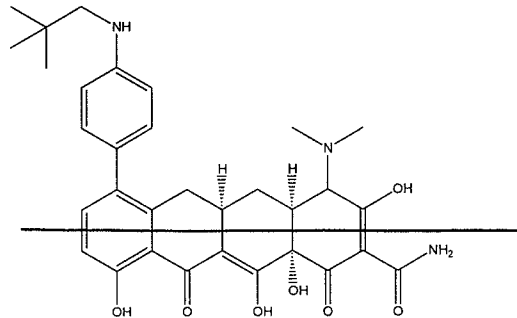
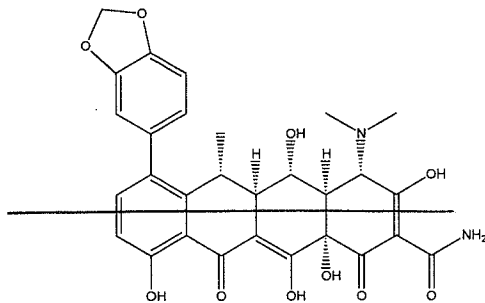
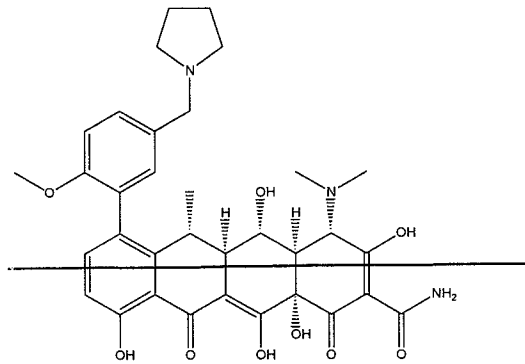
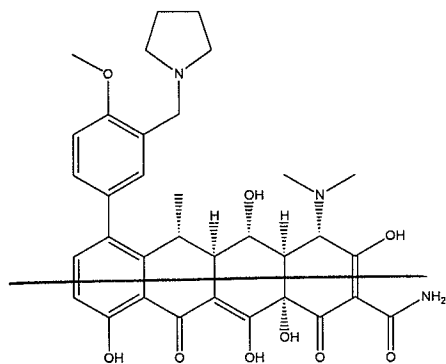




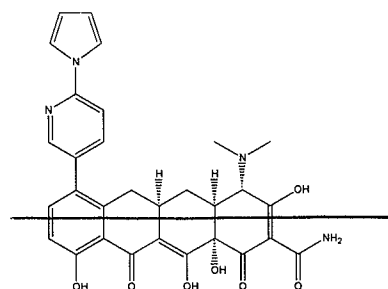
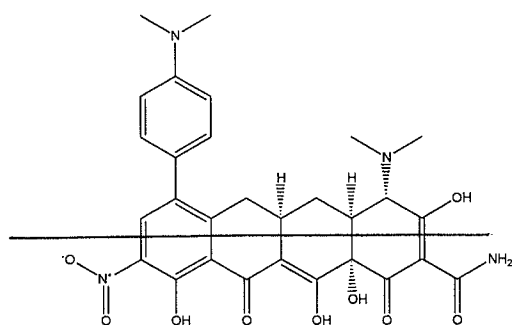
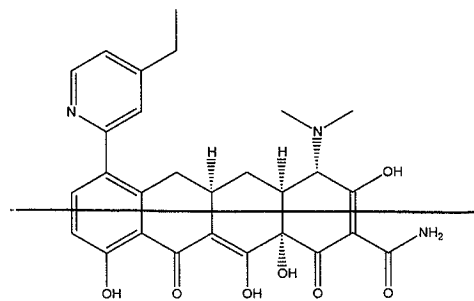
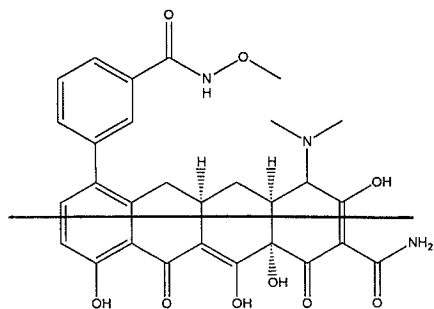
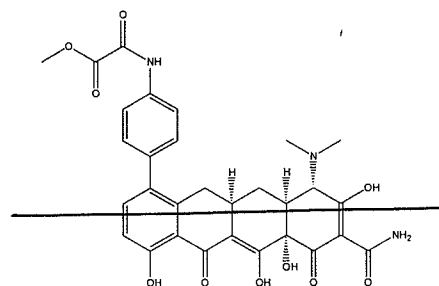
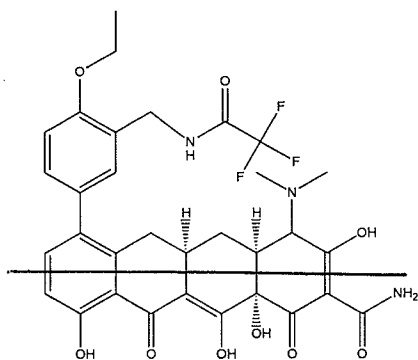
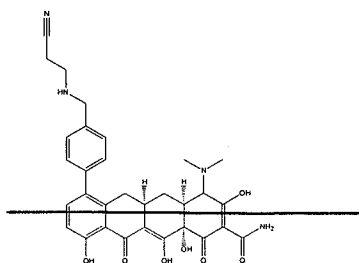
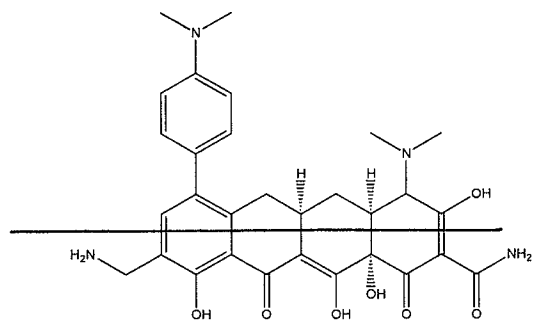
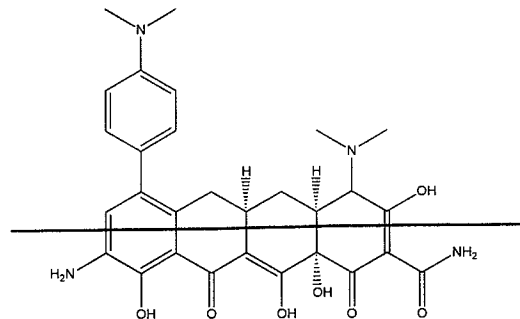
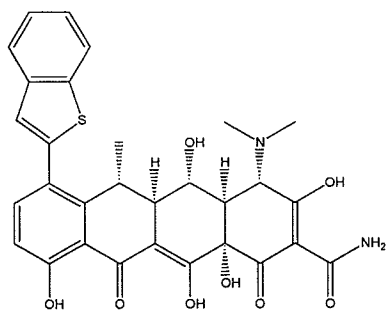


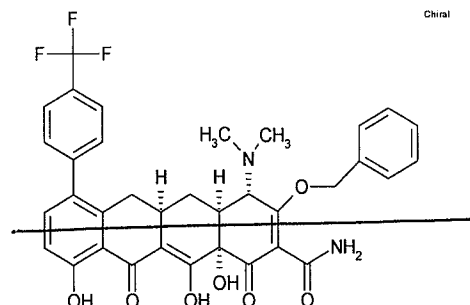
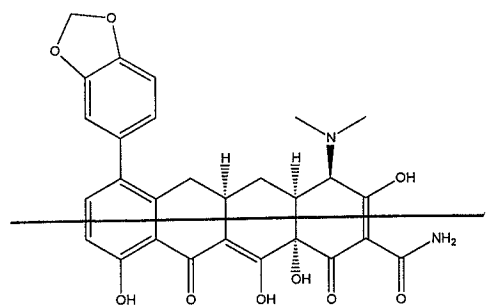




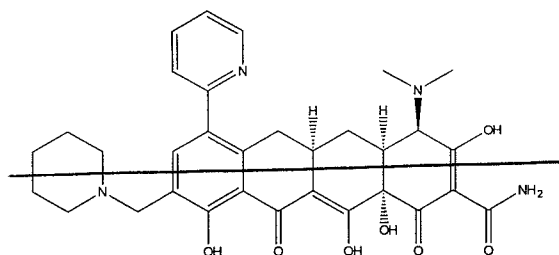
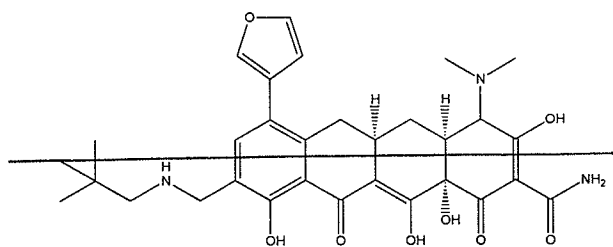


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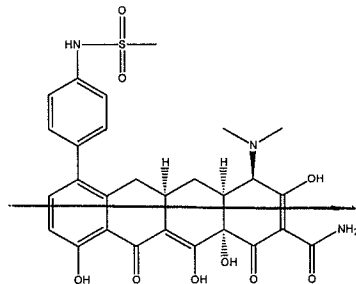
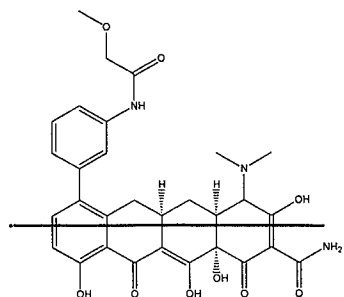
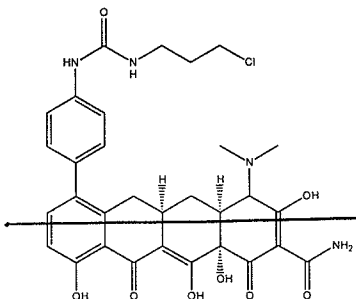
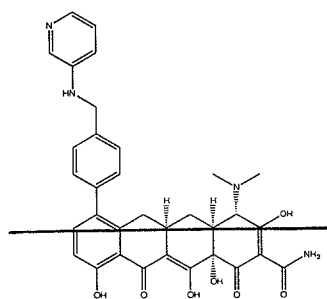
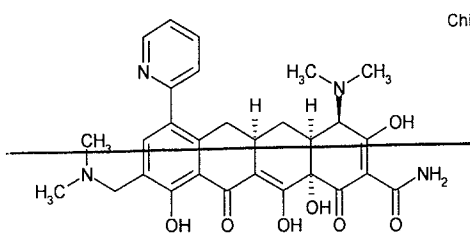
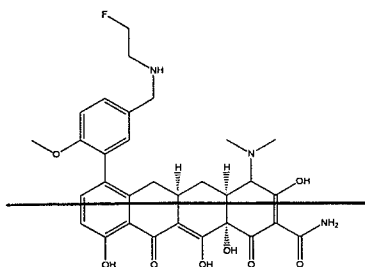




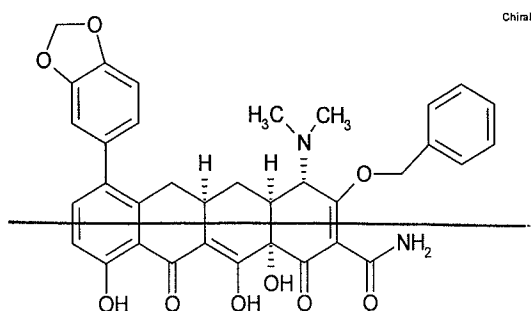
Chiral



Chiral



and



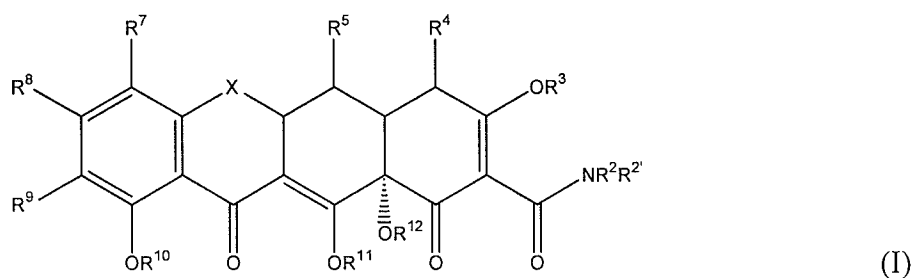
51. **(Original)** The method of claim 1, wherein said subject is a human.
52. **(Original)** The method of claim 1, wherein said substituted tetracycline compound is has anti-microbial gram positive activity.
53. **(Original)** The method of claim 52, wherein said anti-microbial gram positive activity is greater than about 0.05 µg/ml.
54. **(Original)** The method of claim 53, wherein said anti-microbial gram positive activity is greater than about 5 µg/ml.
55. **(Original)** The method of claim 1, wherein said substituted tetracycline compound in non-antibacterial.
56. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a cytotoxicity of 25 µg/ml or greater.
57. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a MIC of 150 nM or less.
58. **(Original)** The method of claim 57, wherein said substituted tetracycline compound has a MIC of 50 nM or less.
59. **(Original)** The method of claim 58, wherein said substituted tetracycline compound has a MIC of 10 nM or less.
60. **(Original)** The method of claim 59, wherein said substituted tetracycline compound has an MIC or 5 nM or less.
61. **(Original)** The method of claim 1, wherein said malaria is caused by a plasmodium protozoan selected from the group consisting of: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*.

62. **(Original)** The method of claim 1, wherein said malaria is resistant to one or more anti-malarial compounds selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, proguanil, and 1,16-hexadecamethylenebis(N-methylpyrrolidinium) dibromide.

63 – 65. **(Canceled)**

66. **(Previously Presented)** The method of claim 1, further comprising administering an anti-malarial compound selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide, and combinations thereof.

67. **(Currently Amended)** A method for increasing the antimalarial activity of an antimalarial compound, comprising administering said antimalarial compound in combination with an effective amount of a substituted tetracycline compound, such that the antimalarial activity of said antimalarial compound is increased, wherein said tetracycline compound is of formula I:



wherein:

X is CR^{6'}R⁶;

R^2 , $R^{2'}$, $R^{4'}$, and $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R^3 , R^{11} and R^{12} are each hydrogen, or a pro-drug moiety;

R^{10} is hydrogen, or a prodrug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

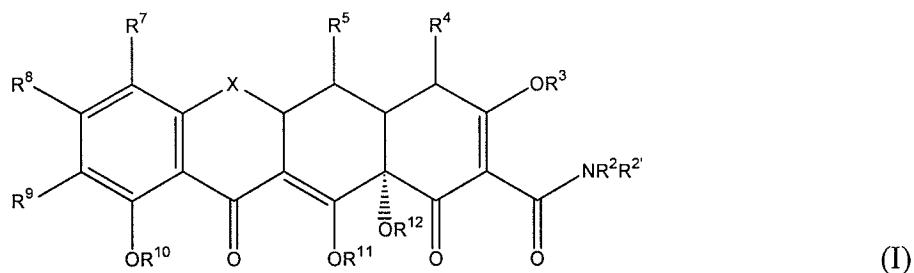
R^7 is aryl, furanyl, benzofuranyl, thienyl, benzothienyl, indolyl, or pyrrolyl;

R^9 is hydrogen; and

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and pharmaceutically acceptable salts thereof.

68. **(Original)** The method of claim 67, wherein said anti-malarial compound is selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide, and combinations thereof.

69. **(Currently Amended)** A method for preventing malaria in a mammal, comprising administering to said mammal an effective amount of a substituted tetracycline compound, such that malaria is prevented in said mammal, wherein said tetracycline compound is of formula I:



wherein:

X is CR^{6'}R⁶;

R², R^{2'}, R^{4'}, and R^{4''} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R⁴ is NR^{4'}R^{4''}, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R³, R¹¹ and R¹² are each hydrogen, or a pro-drug moiety;

R¹⁰ is hydrogen, or a prodrug moiety;

R⁵ is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

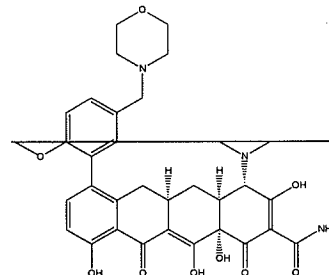
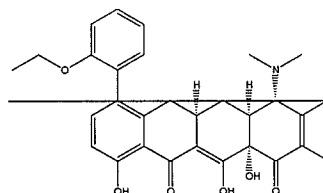
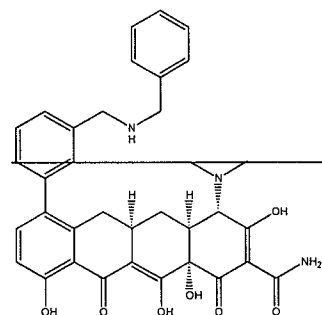
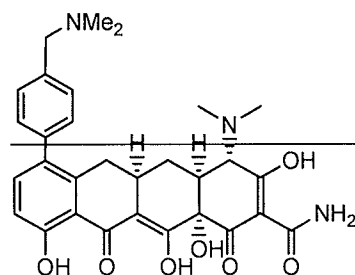
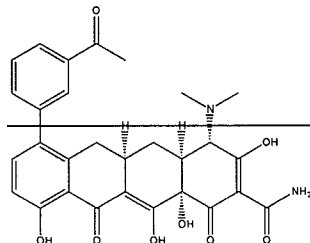
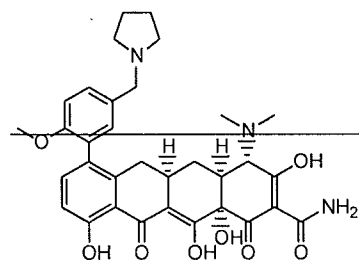
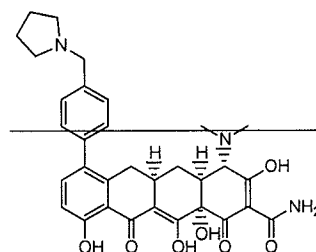
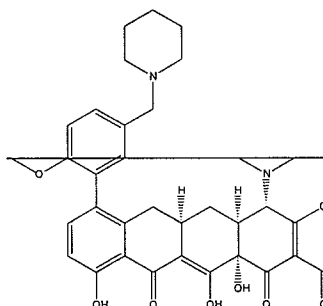
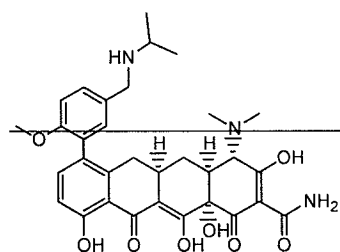
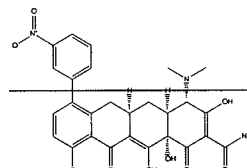
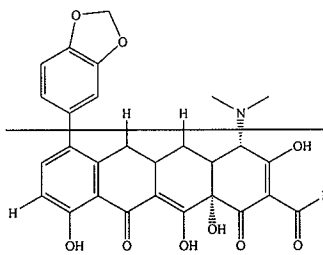
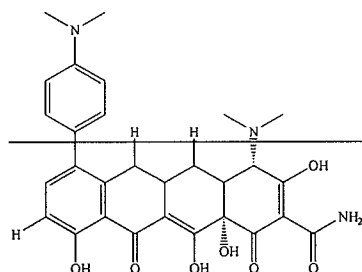
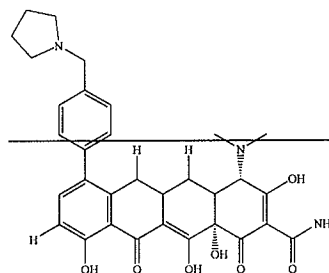
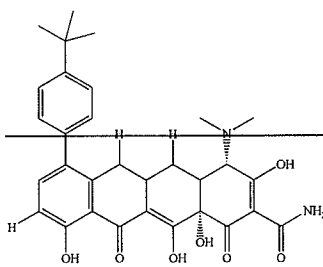
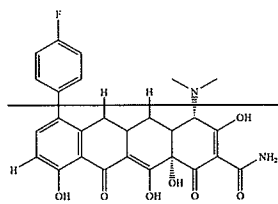
R⁶ and R^{6'} are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

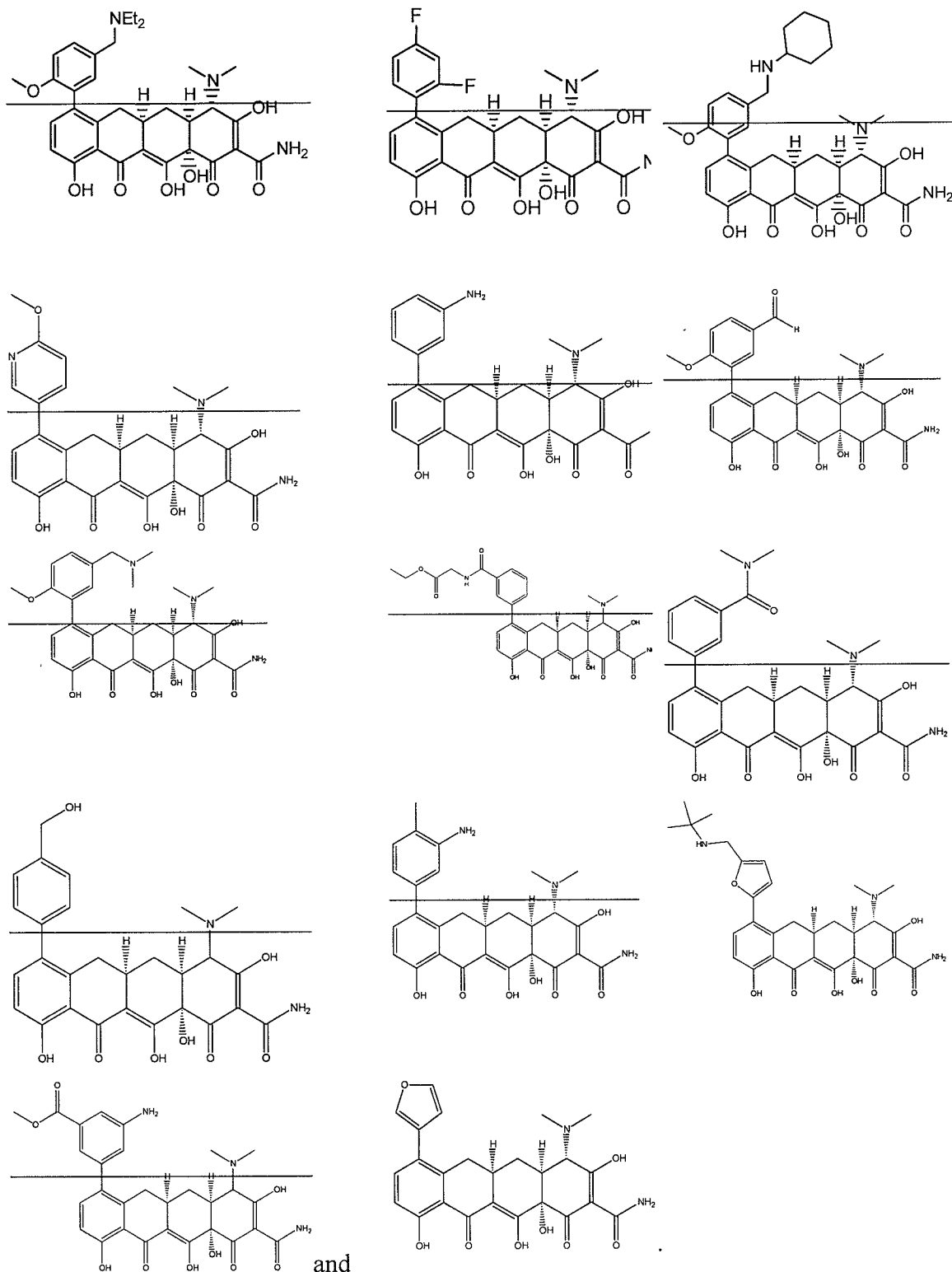
R⁷ is aryl, furanyl, benzofuranyl, thienyl, benzothienyl, indolyl, or pyrrolyl

R⁹ is hydrogen; and

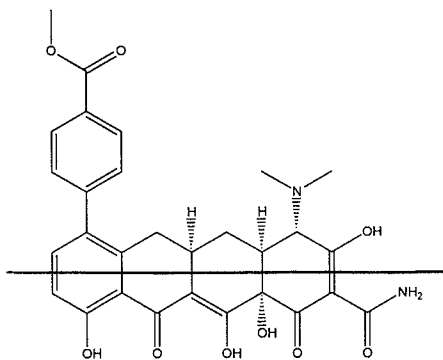
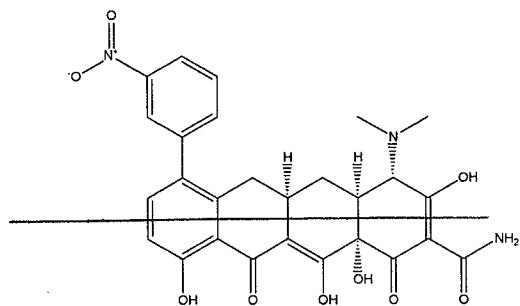
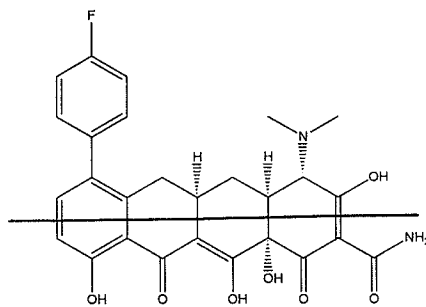
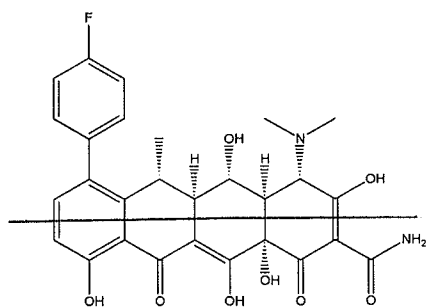
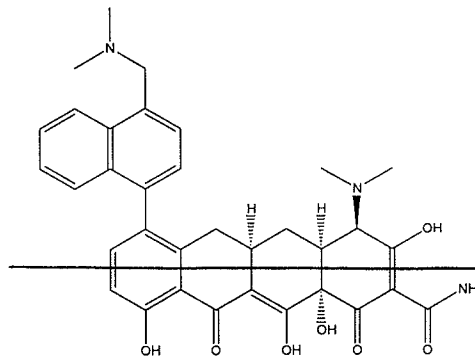
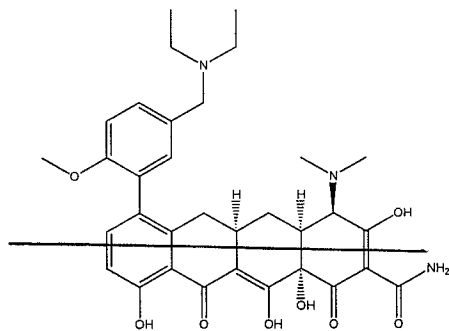
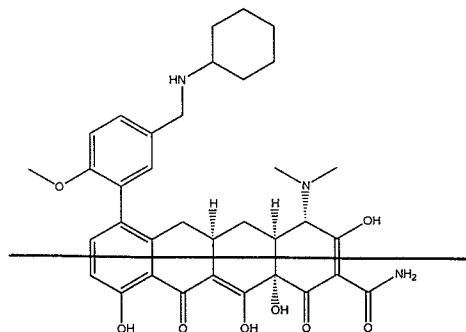
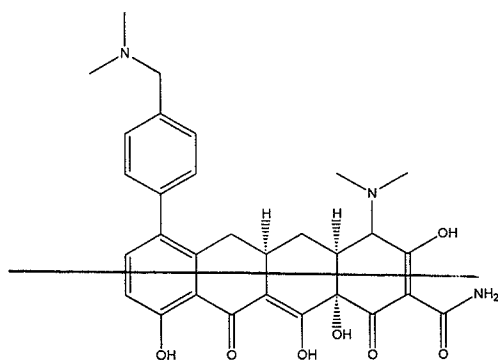
R⁸ is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and pharmaceutically acceptable salts thereof.

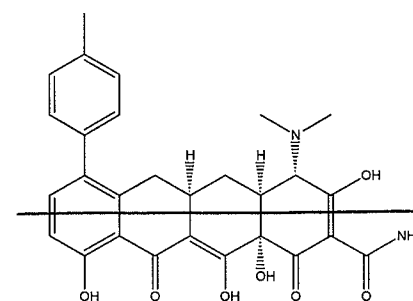
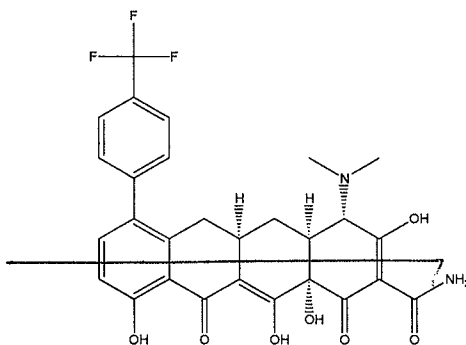
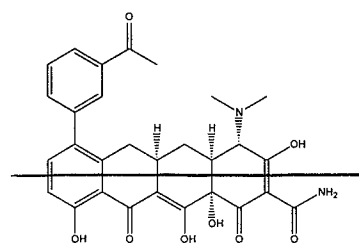
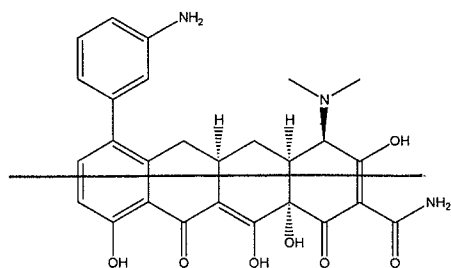
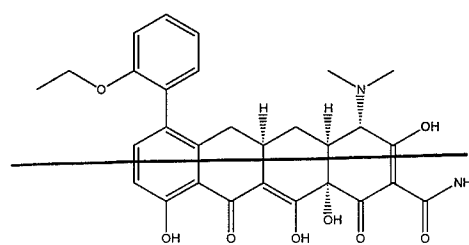
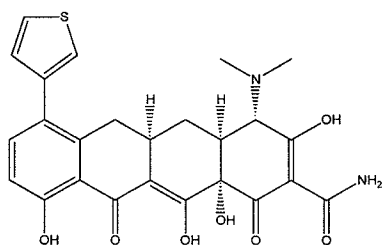
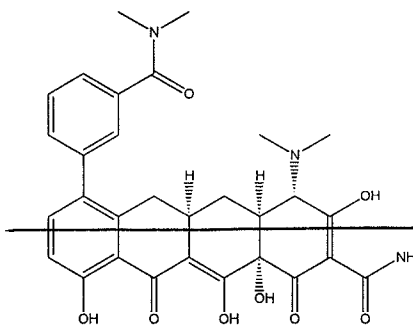
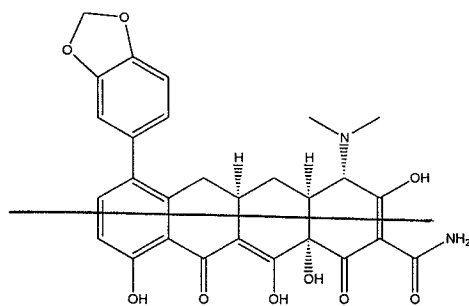
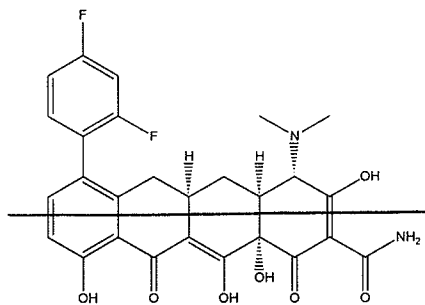
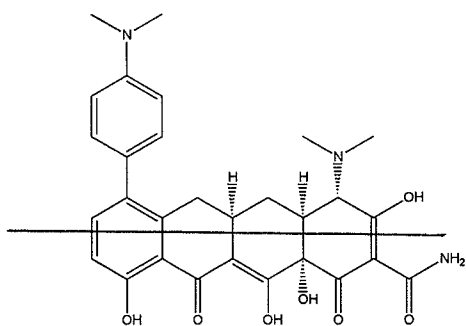
70. **(Currently Amended)** The method of claim 69, wherein said substituted tetracycline compound is selected from the group consisting of:

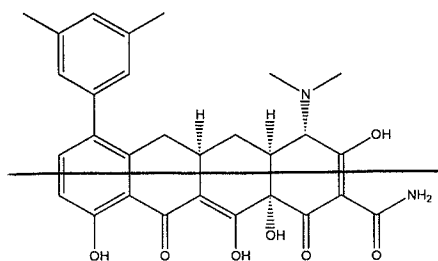
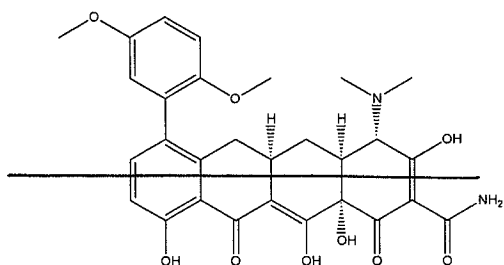
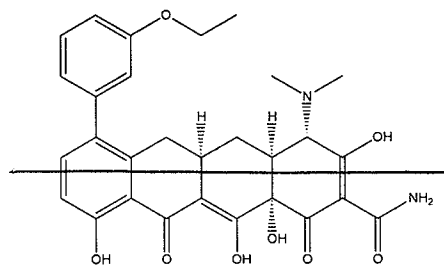
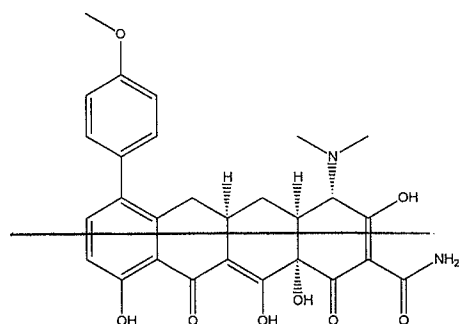
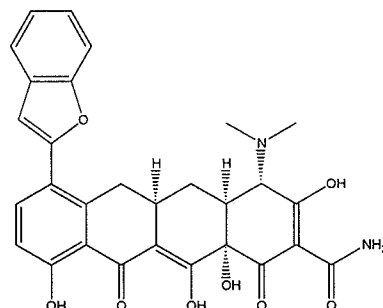
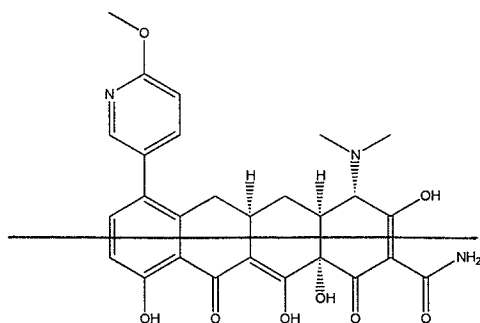
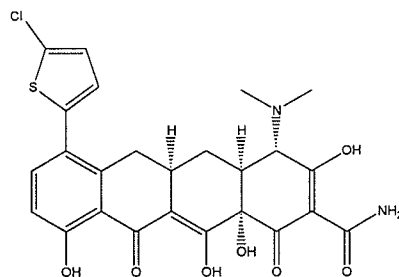
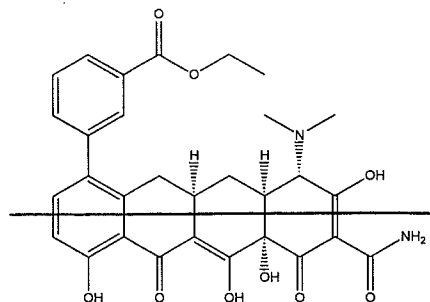
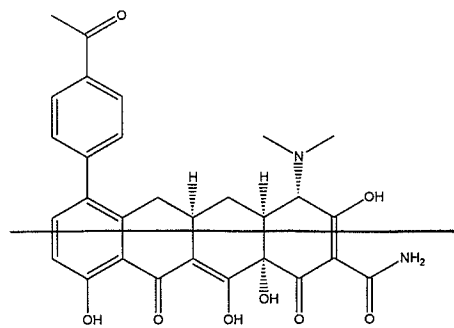
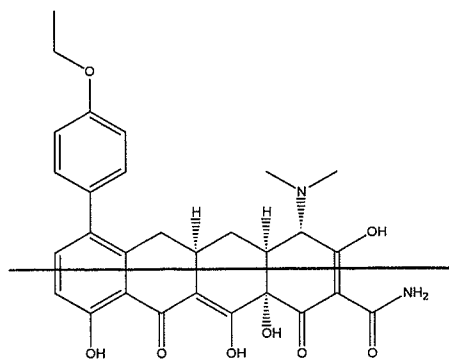


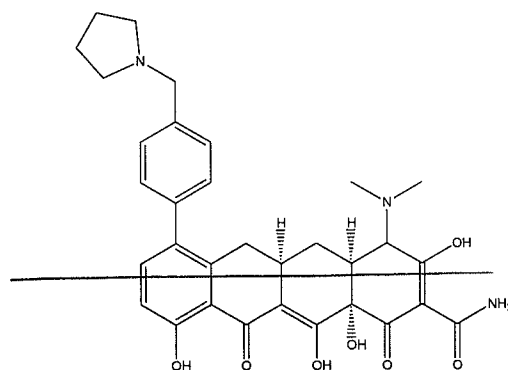
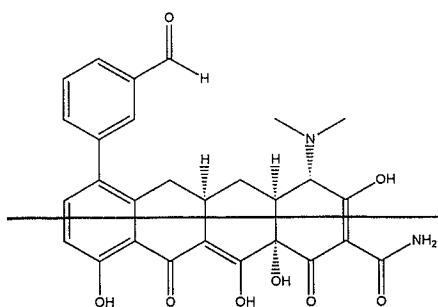
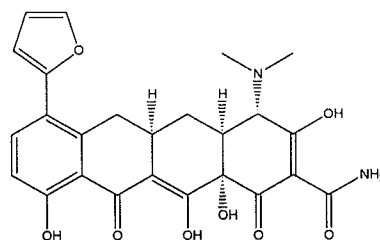
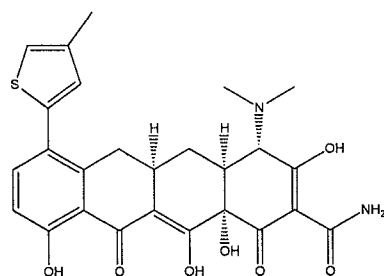
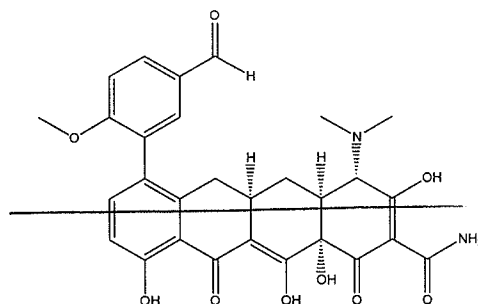
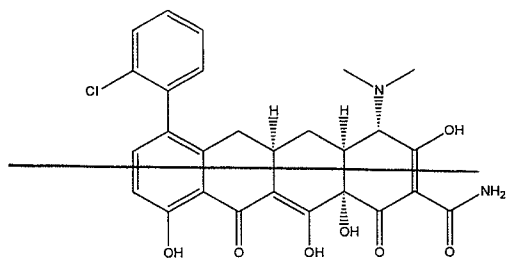
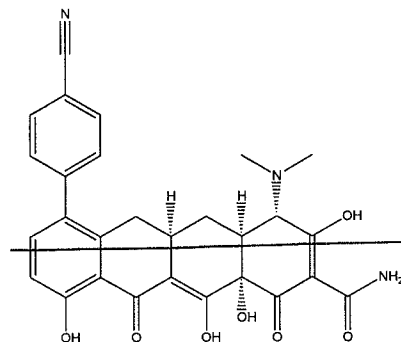
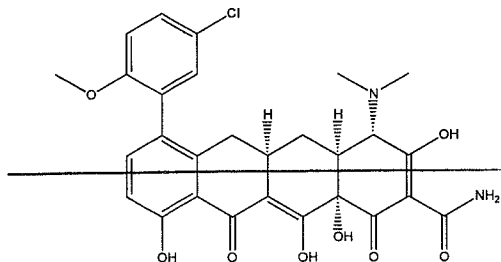
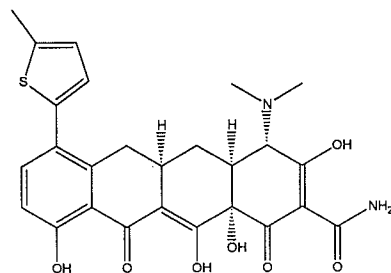
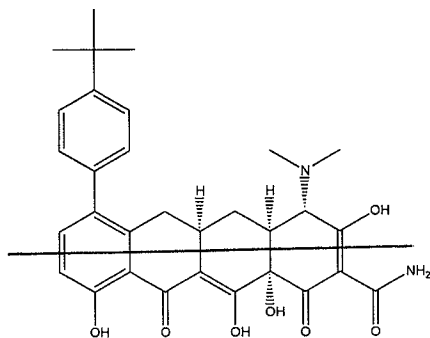


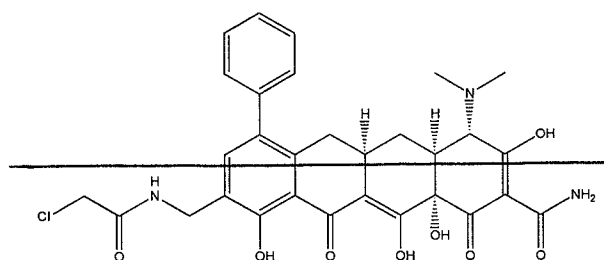
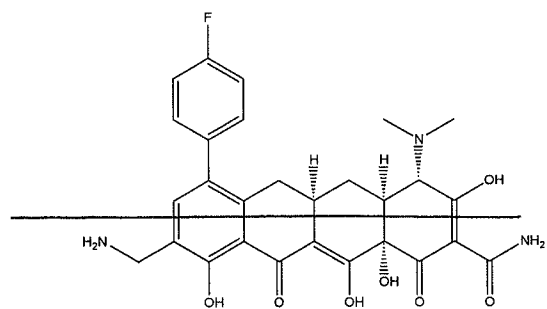
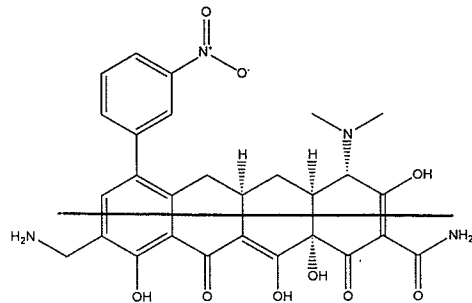
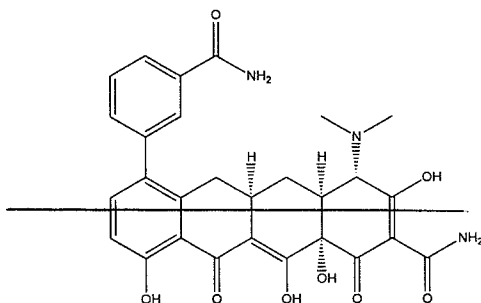
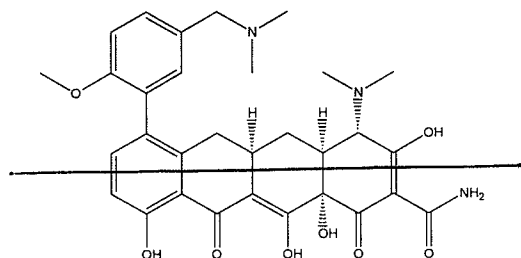
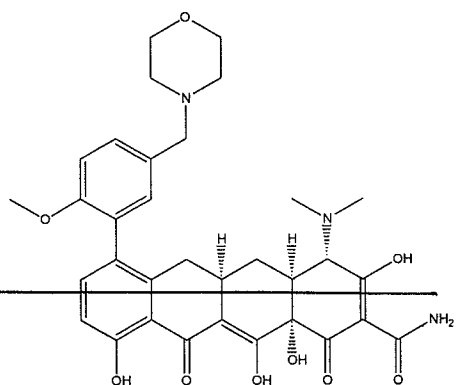
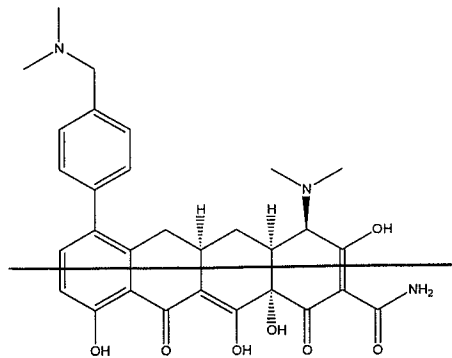
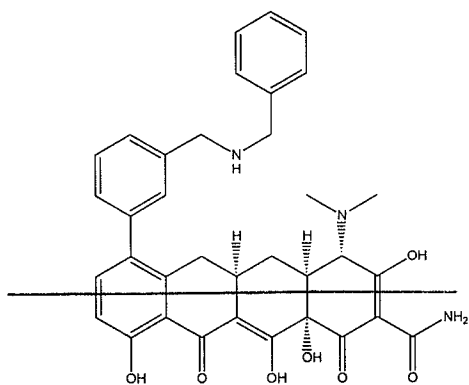
71. **(Currently Amended)** The method of claim 67 or 69, wherein said substituted tetracycline compound is selected from the group consisting of:

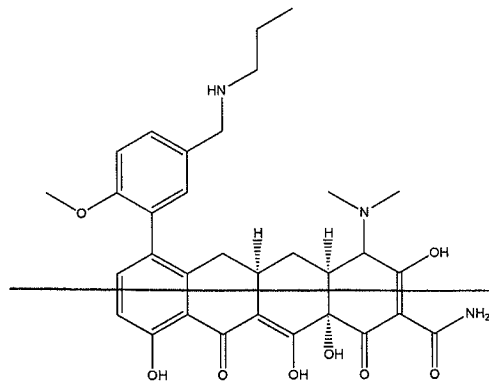
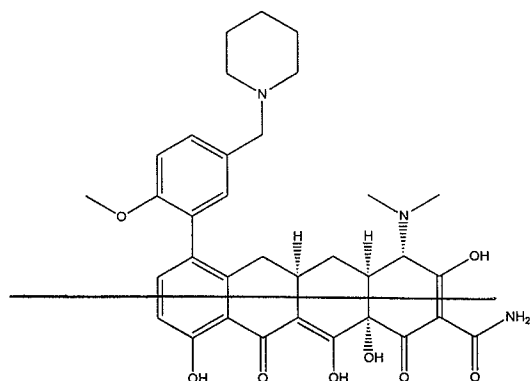
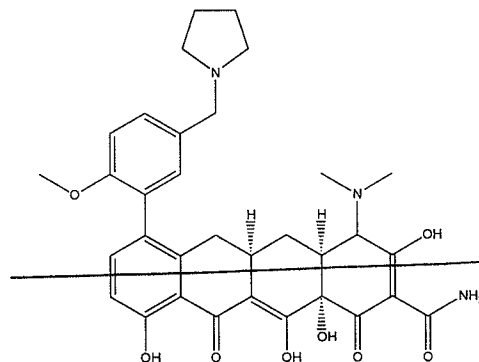
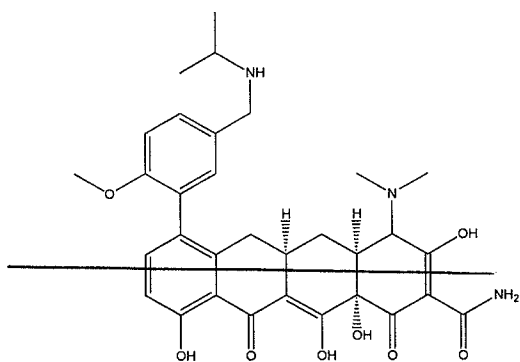
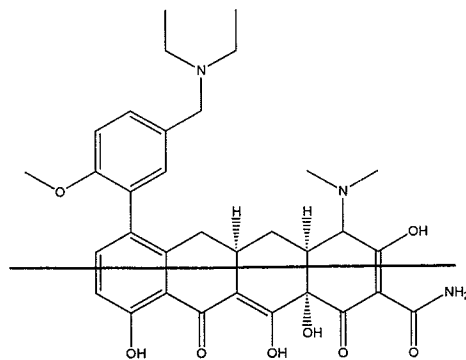
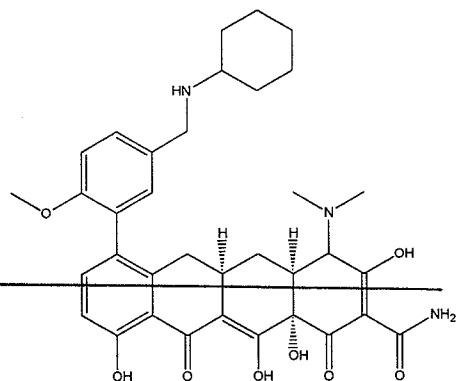
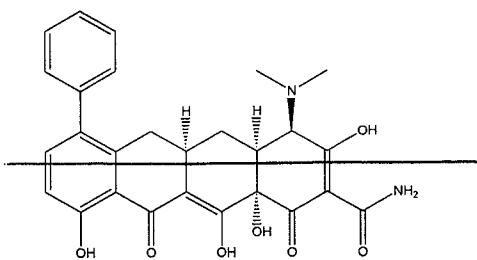
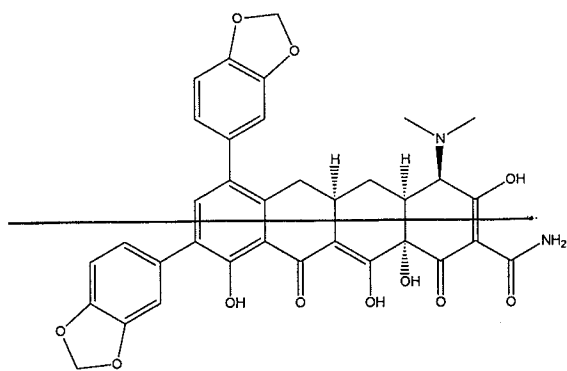


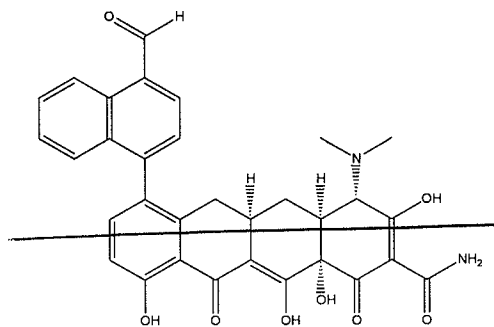
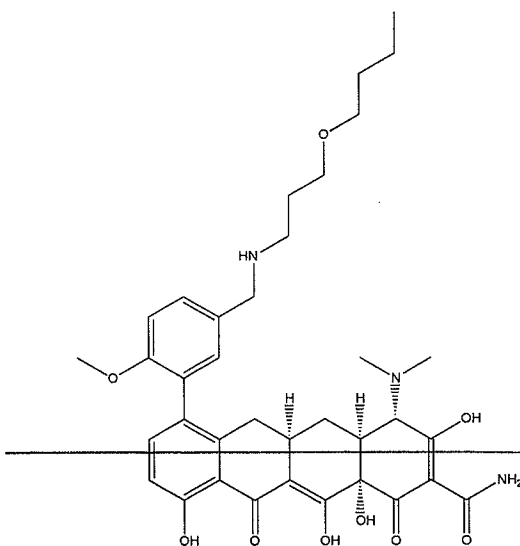
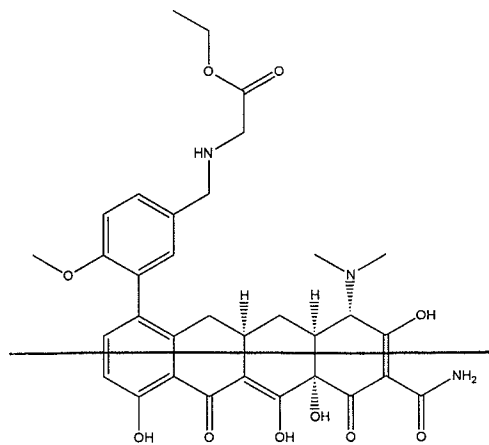
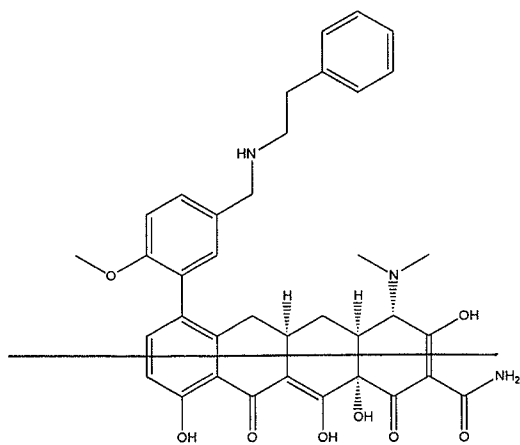
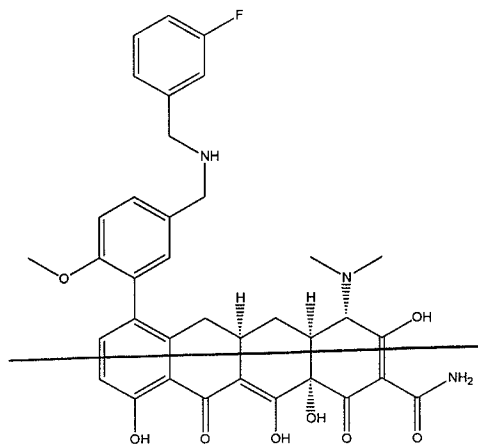
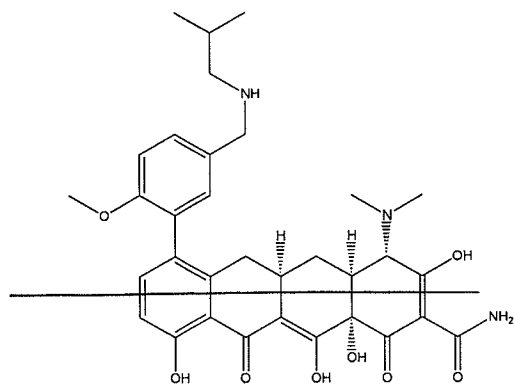


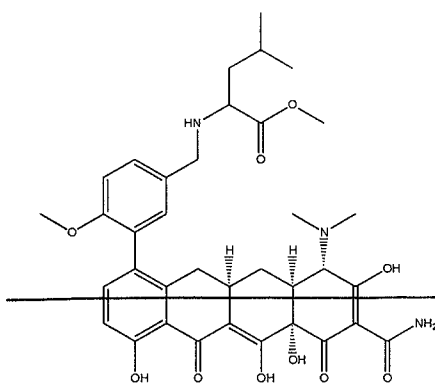
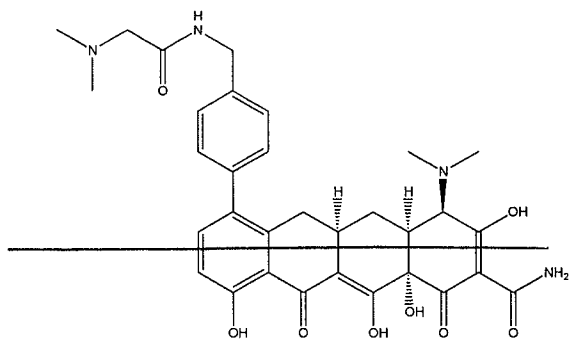
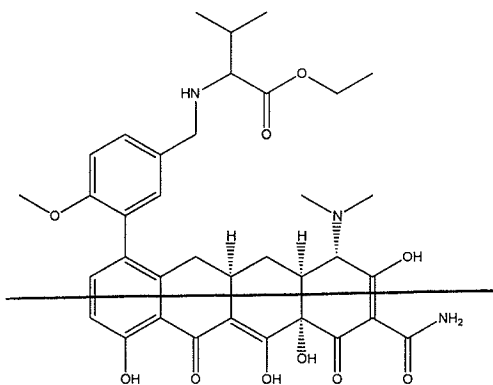
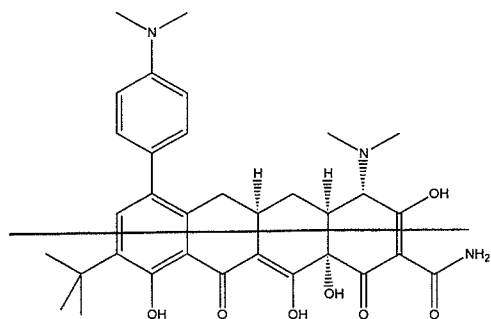
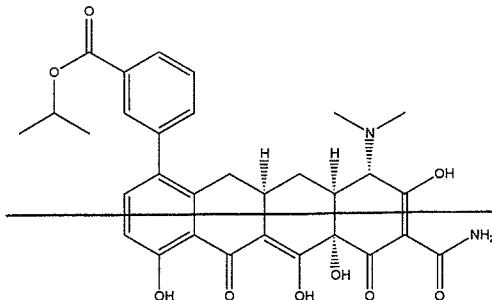
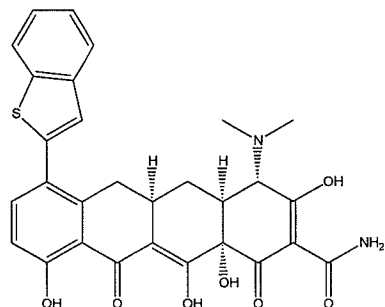
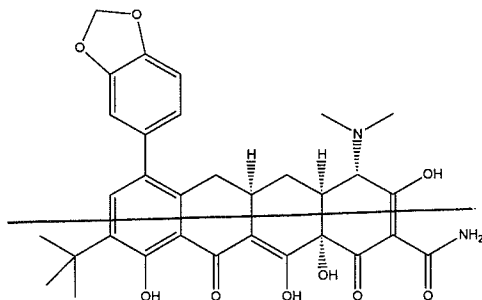
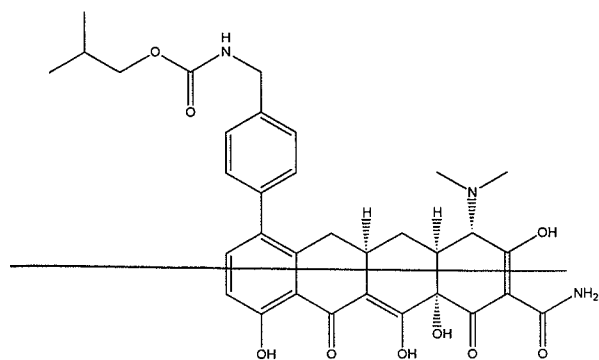


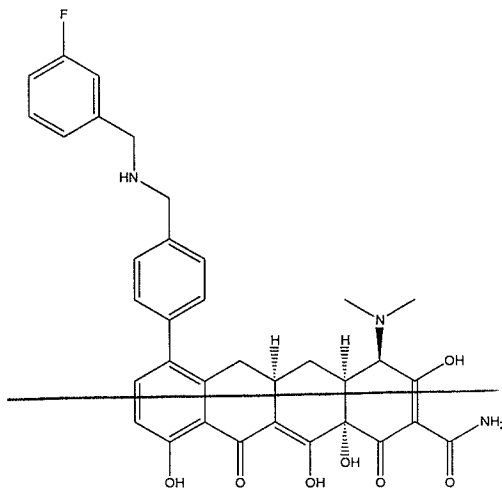
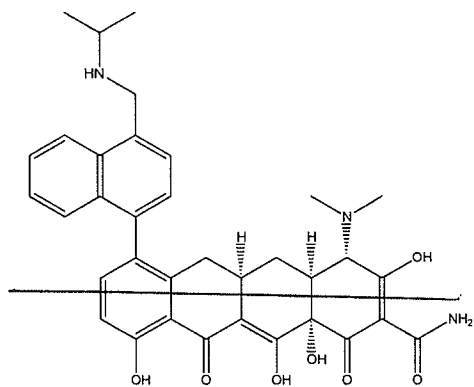
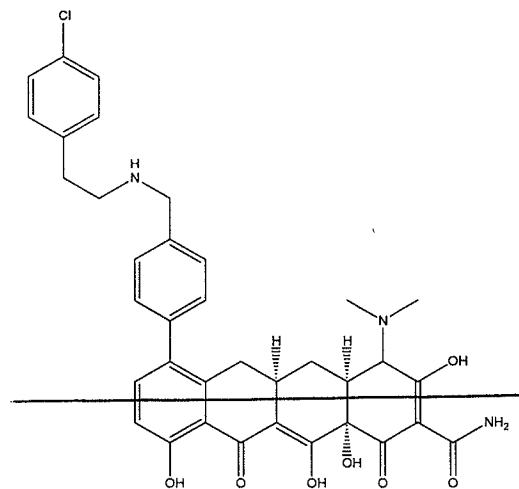
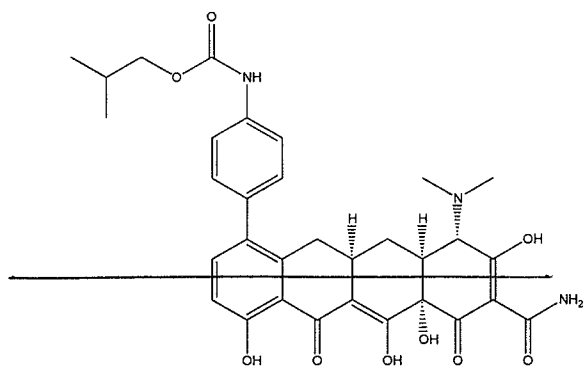
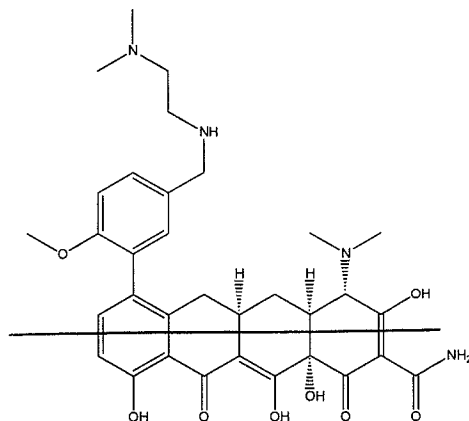
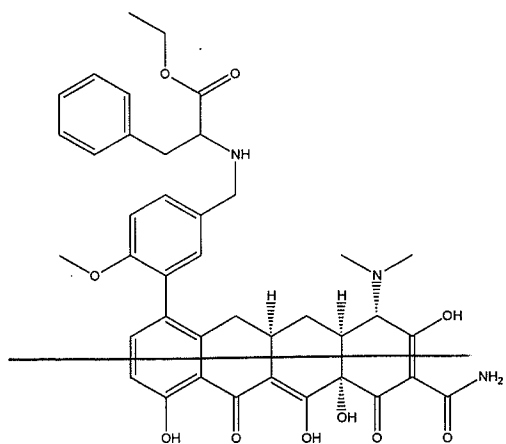


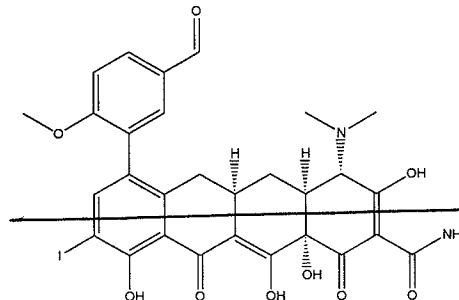
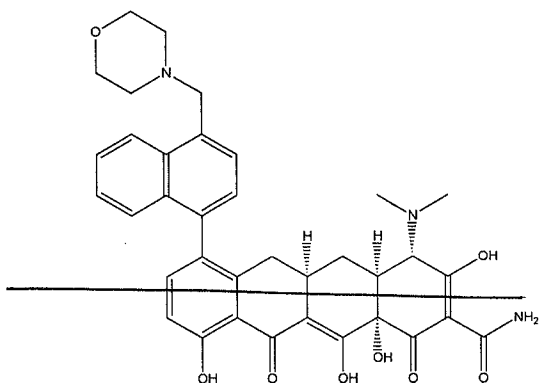
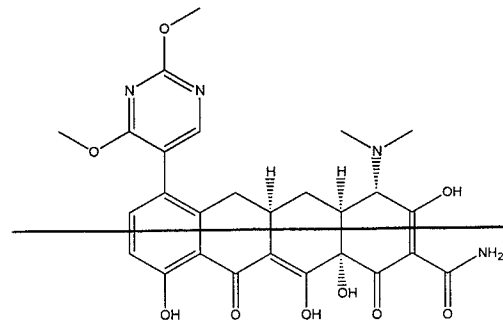
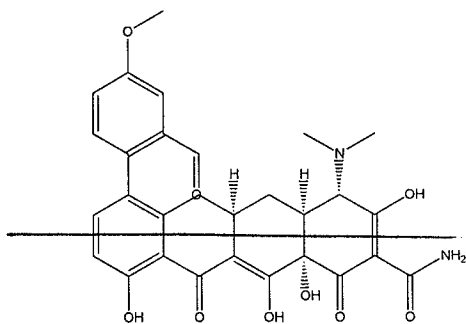
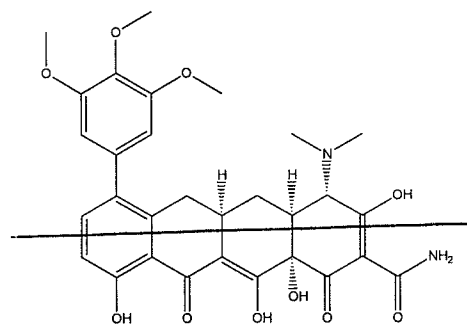
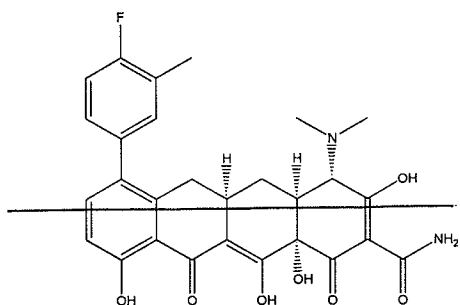
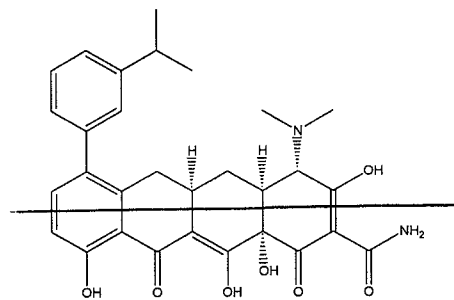
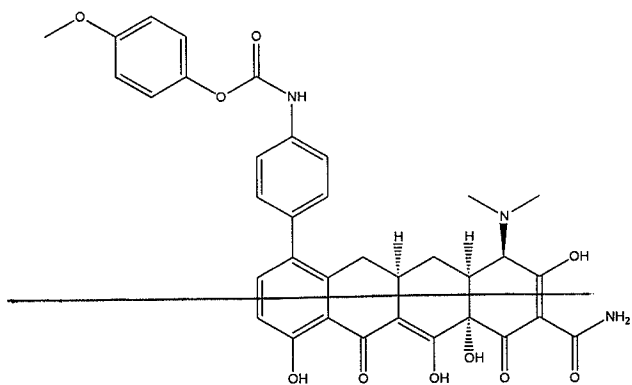


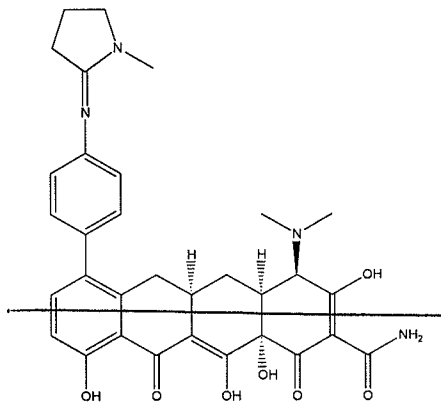
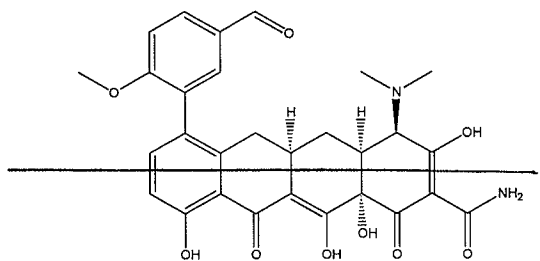
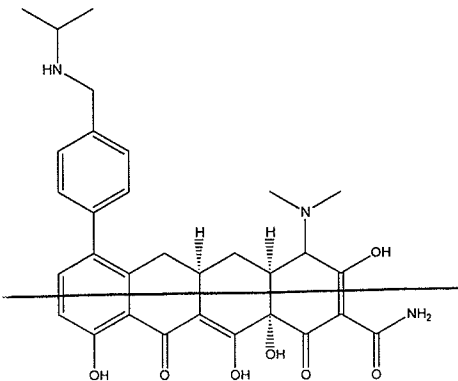
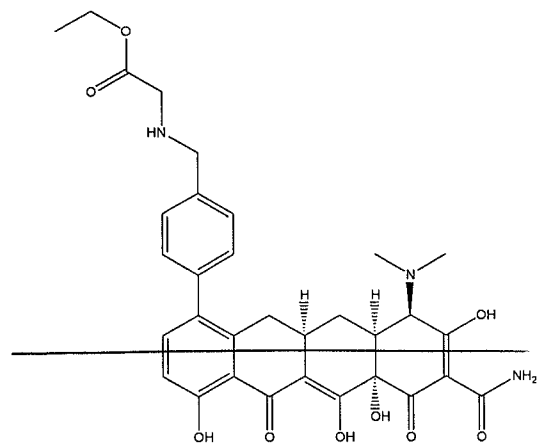
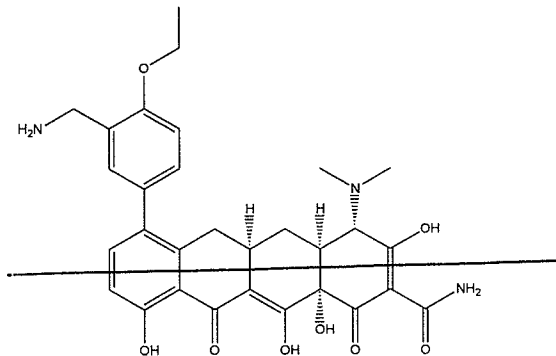
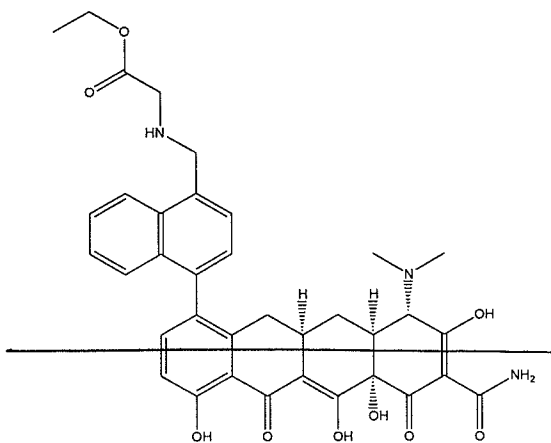
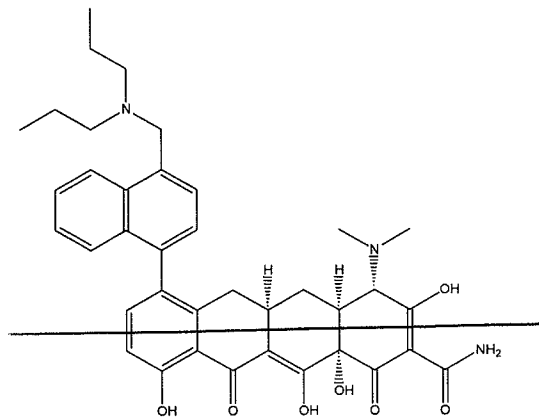
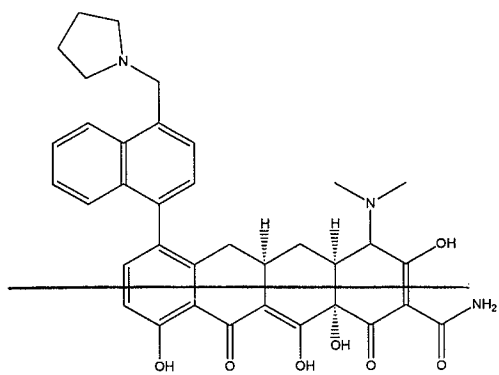


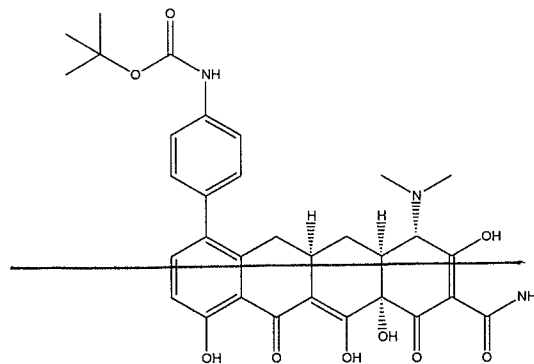
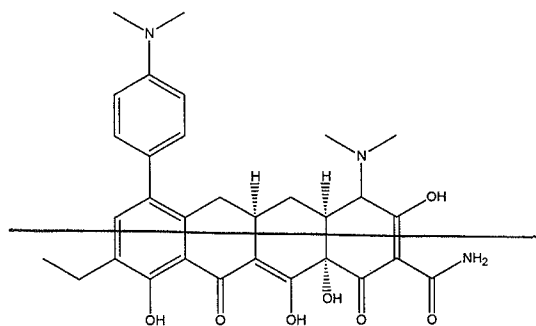
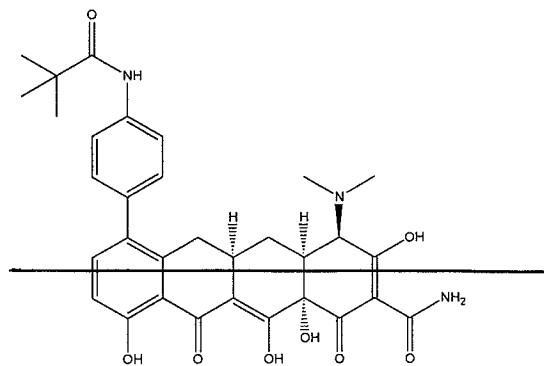
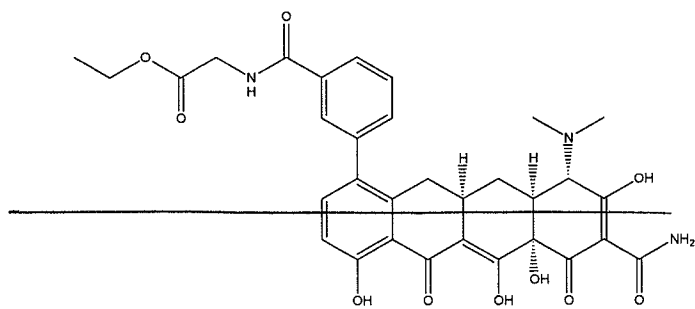
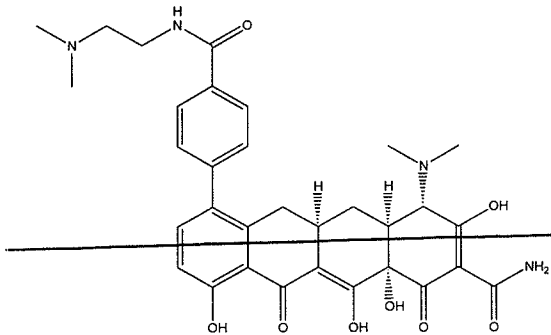
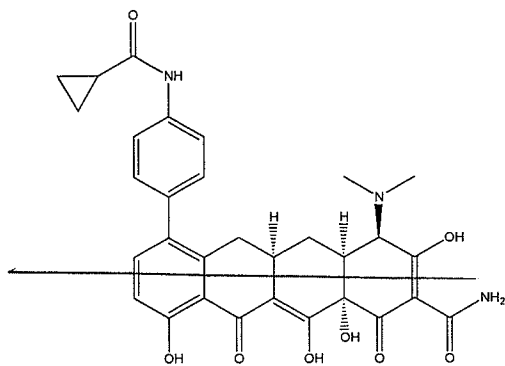
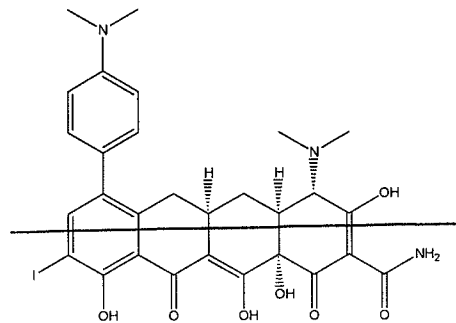
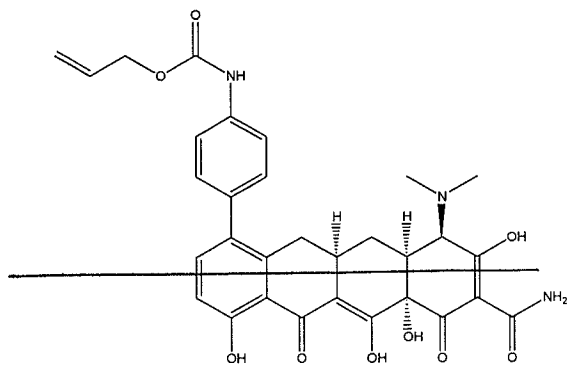


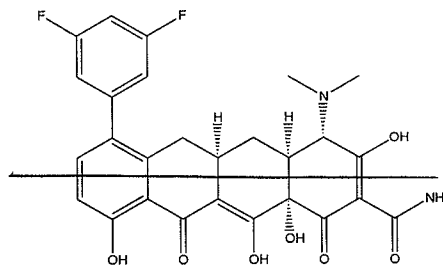
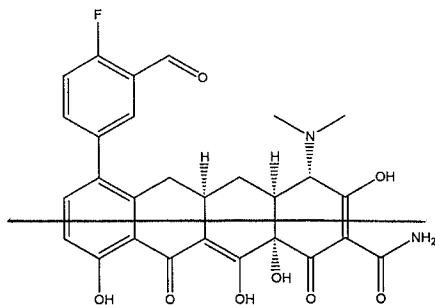
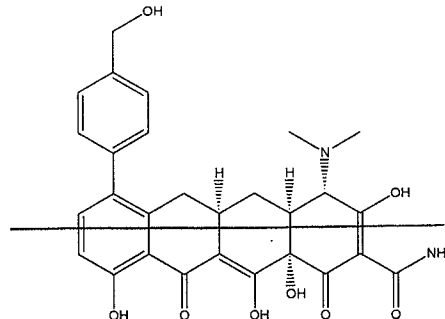
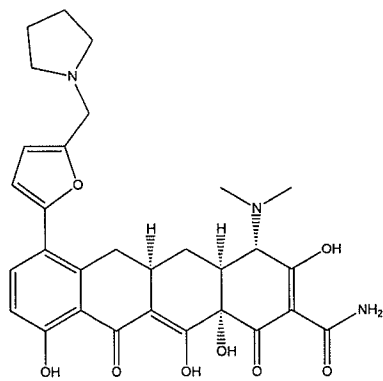
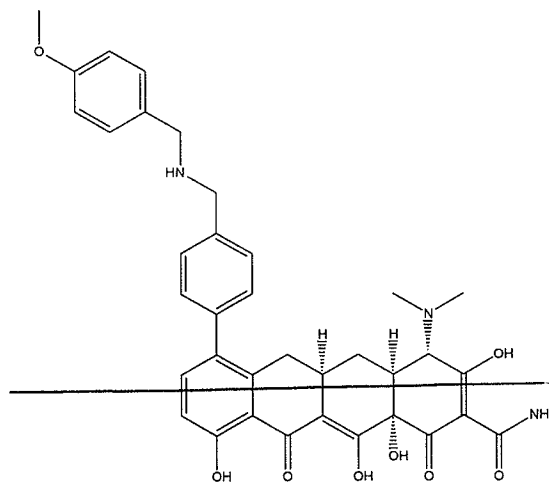
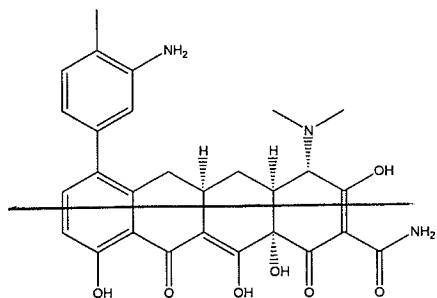
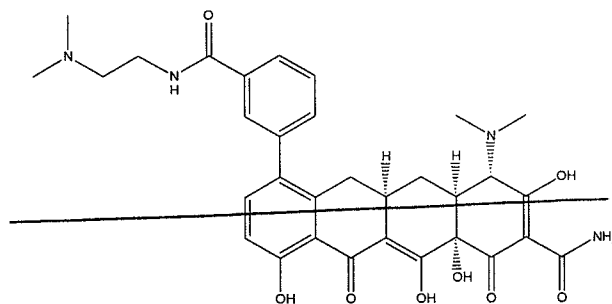
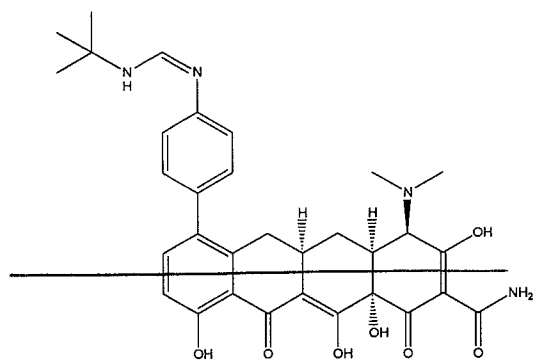


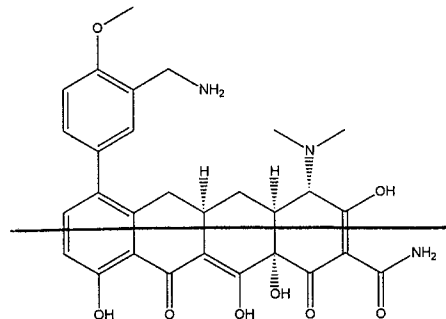
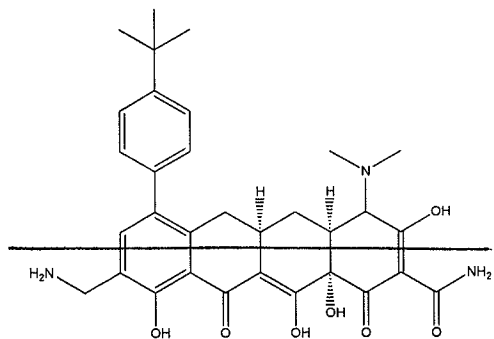
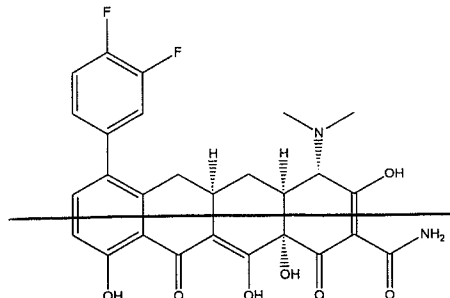
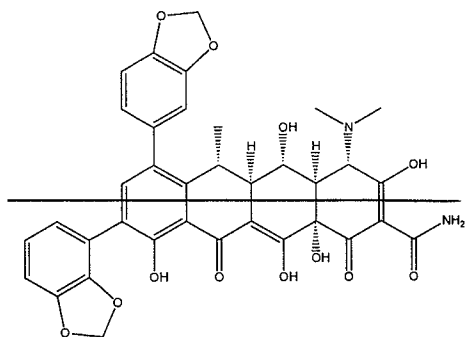
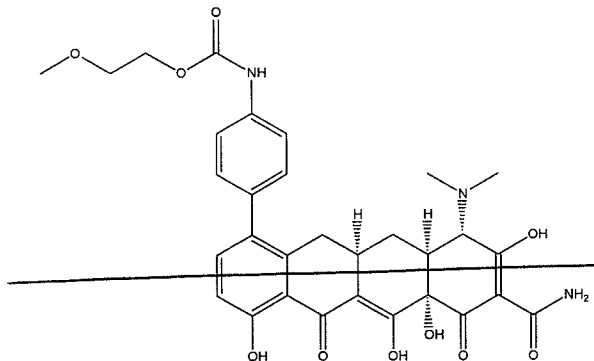
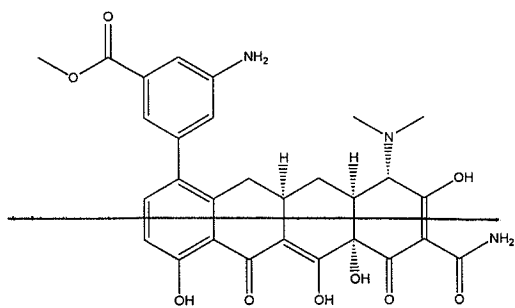
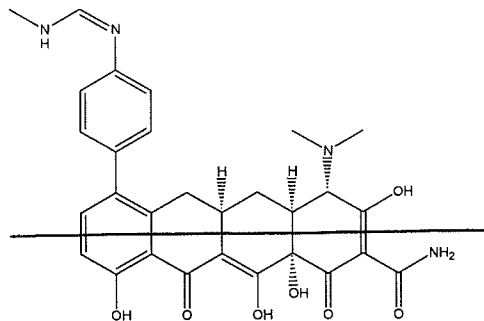
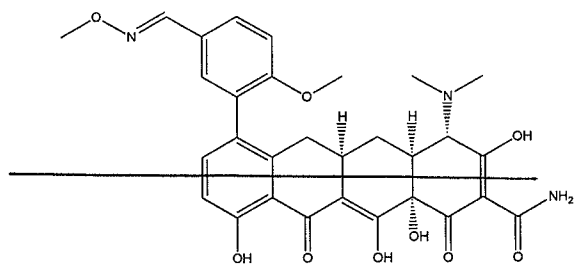


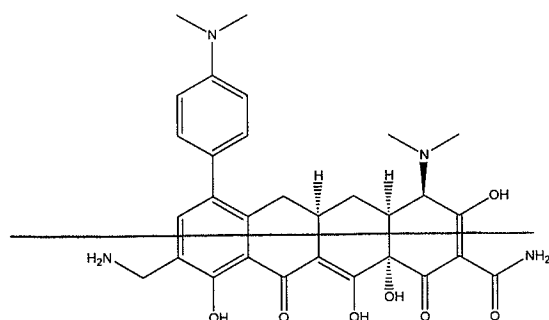
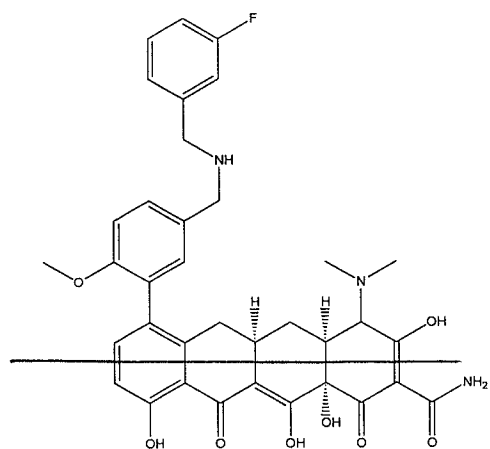
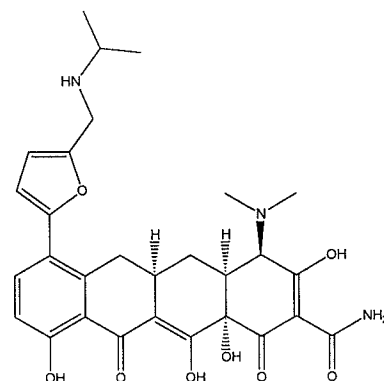
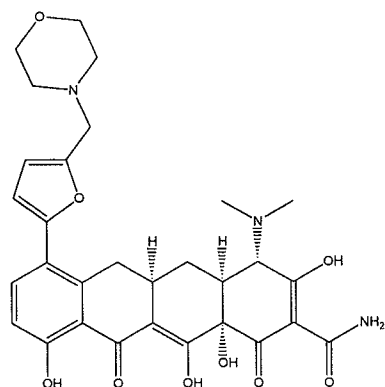
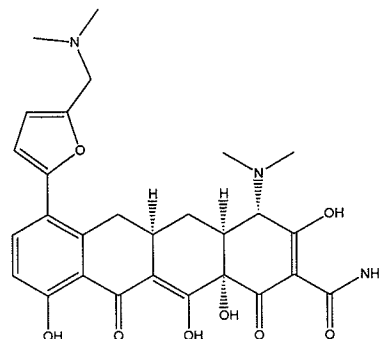
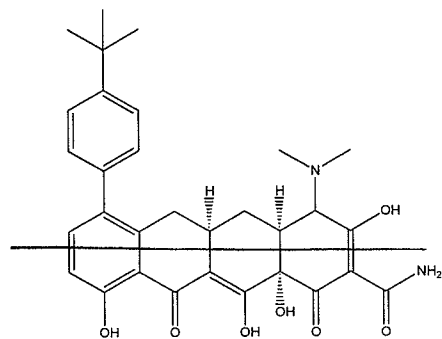
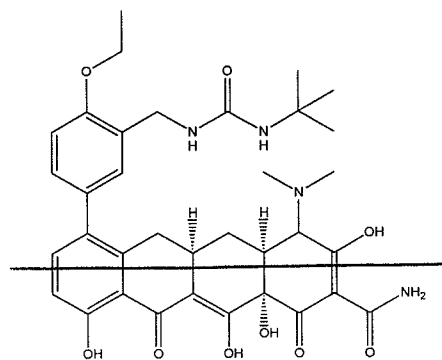
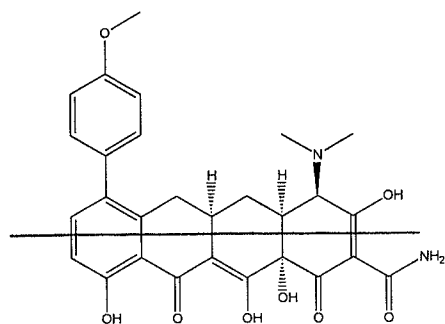


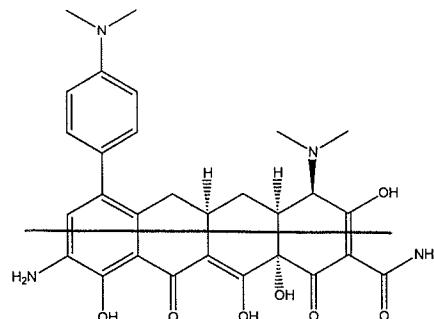
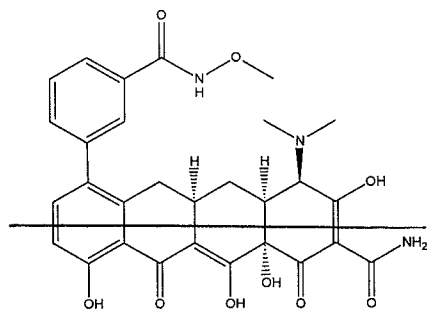
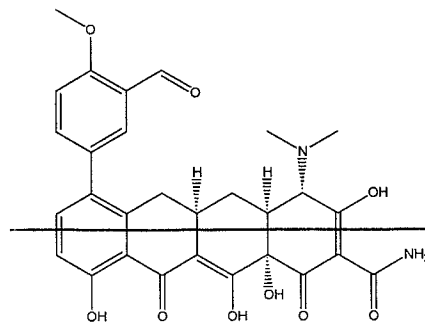
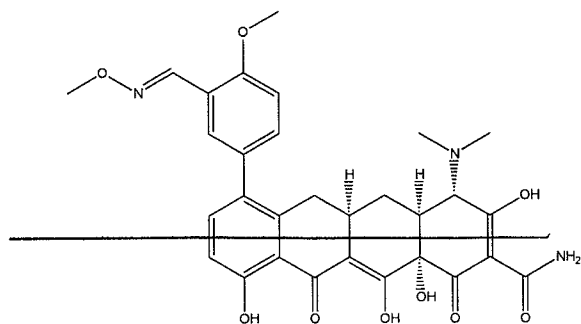
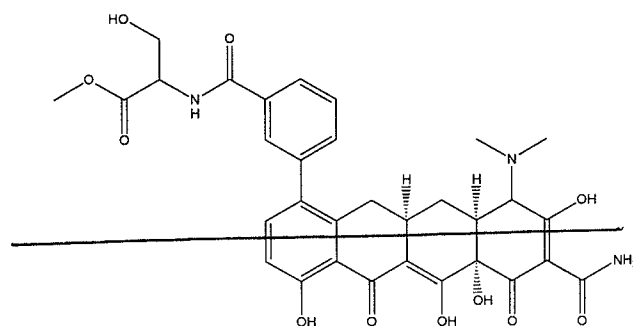
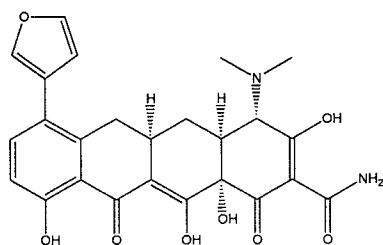
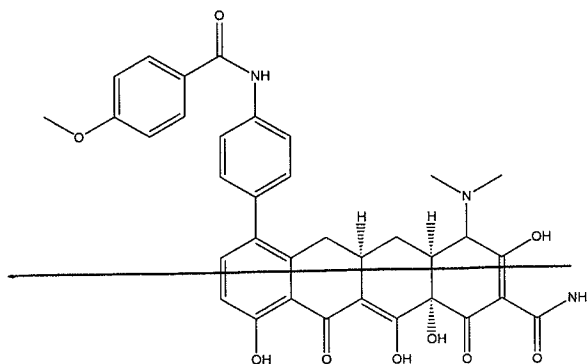
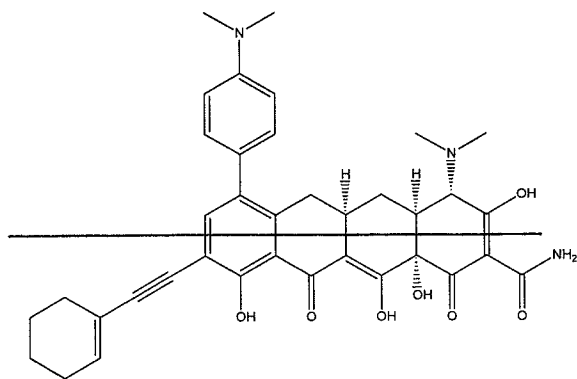


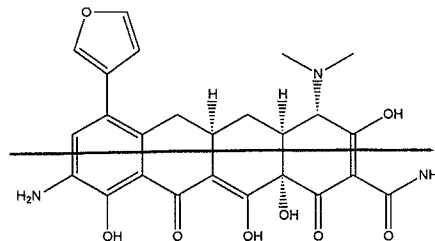
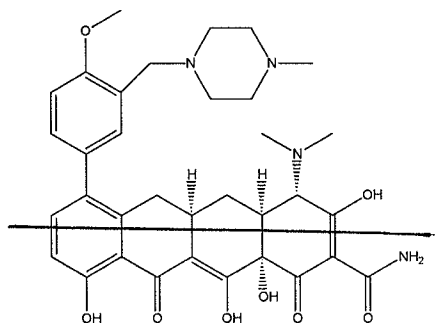
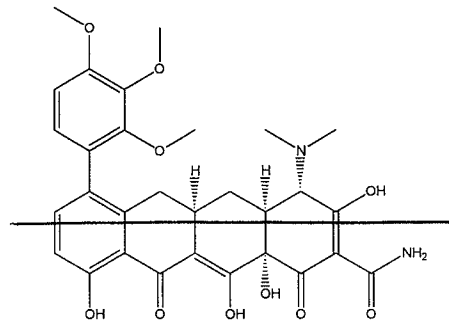
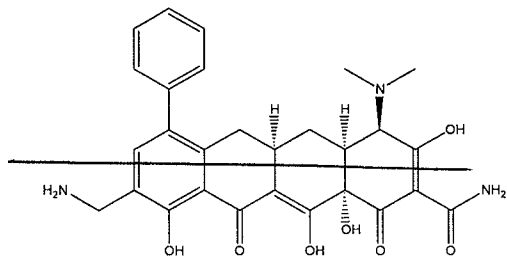
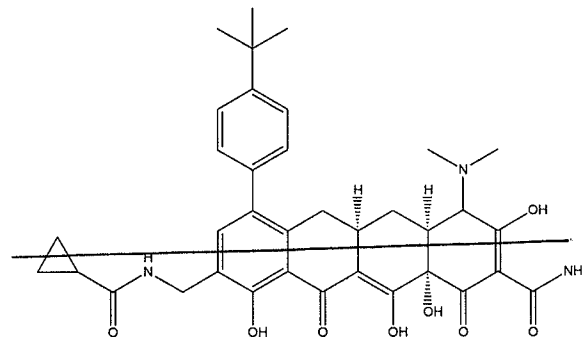
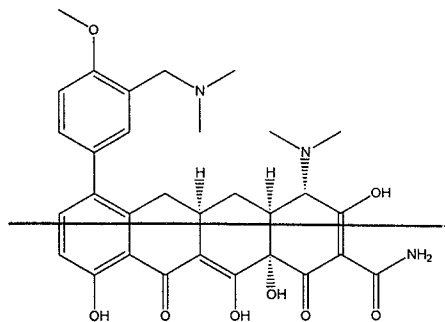
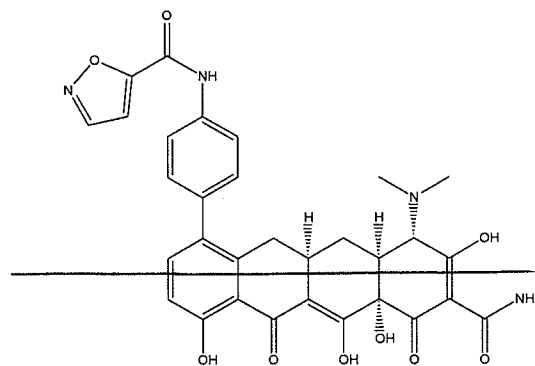
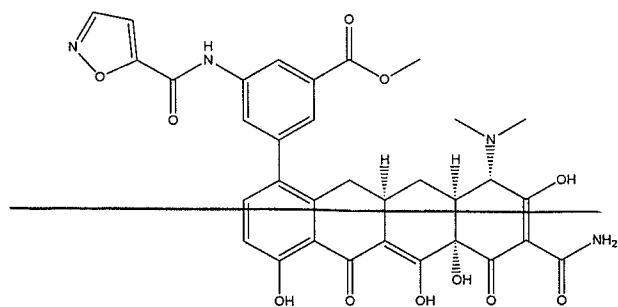


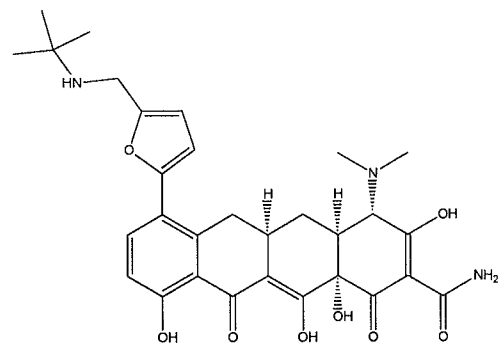
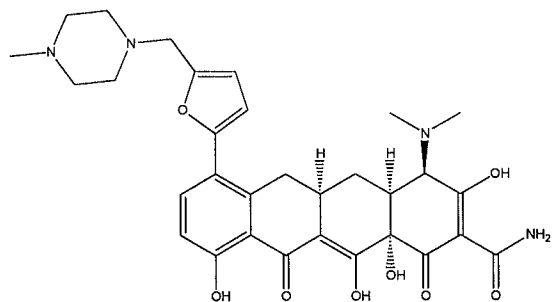
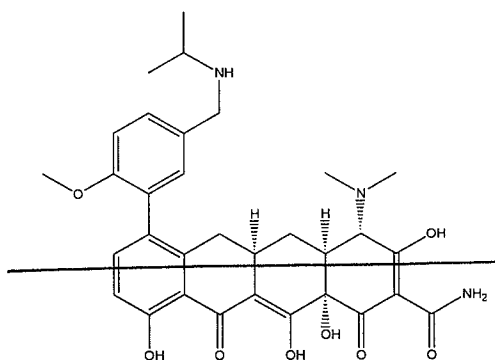
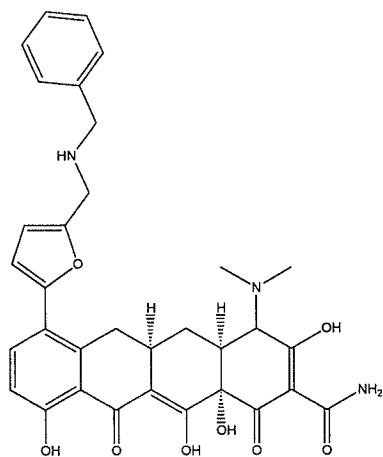
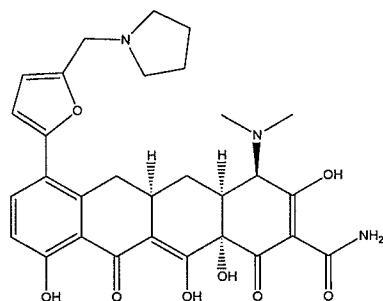
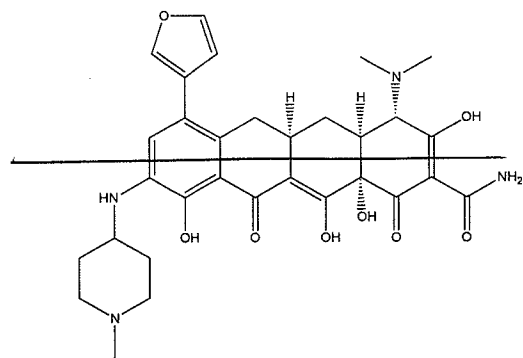
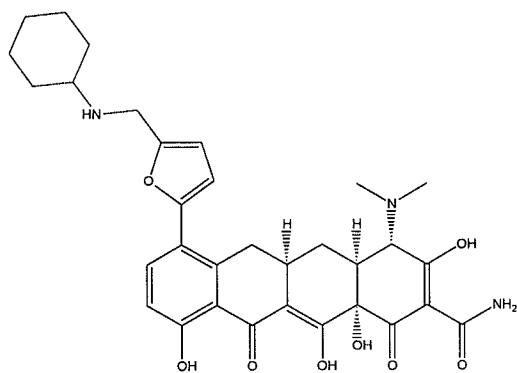
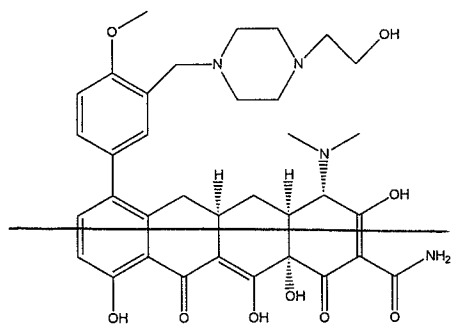


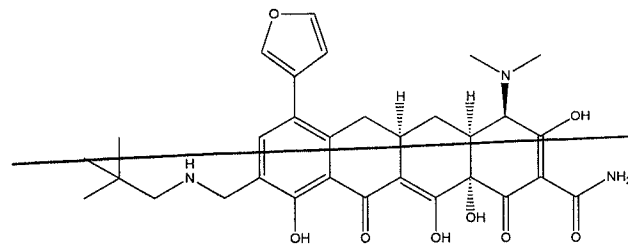
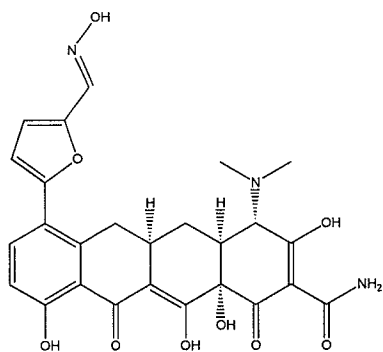
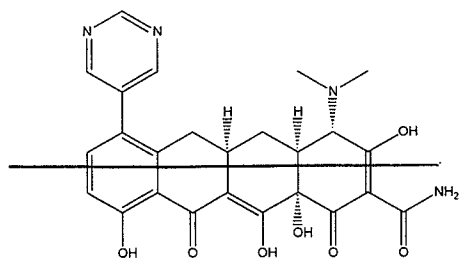
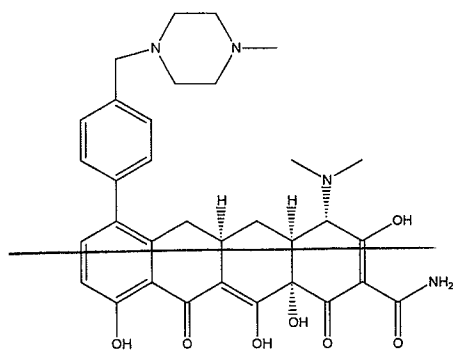
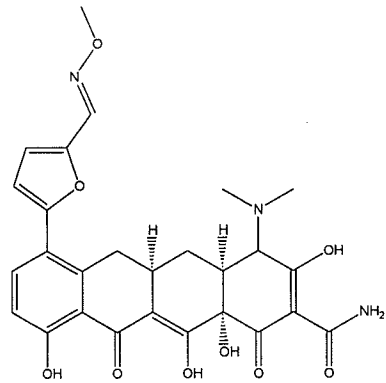
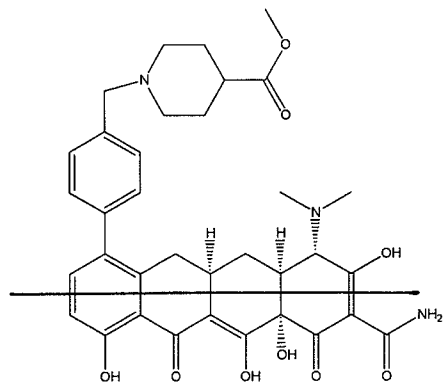
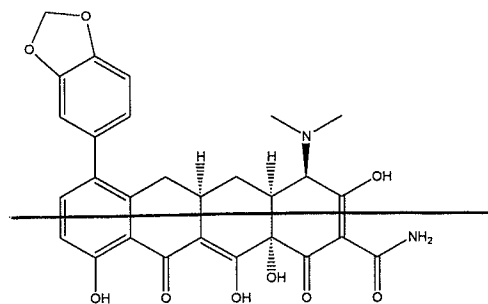
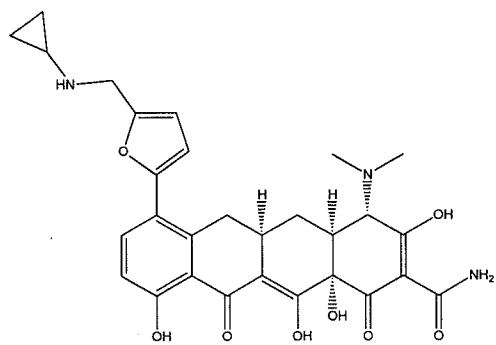


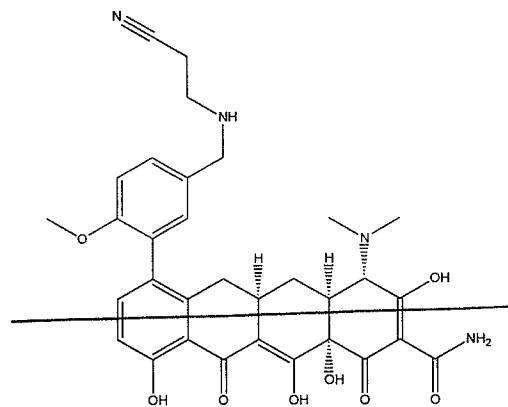
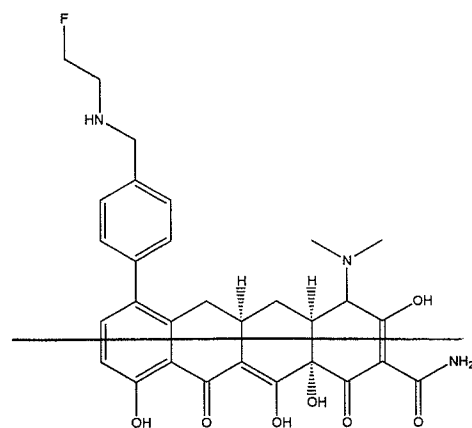
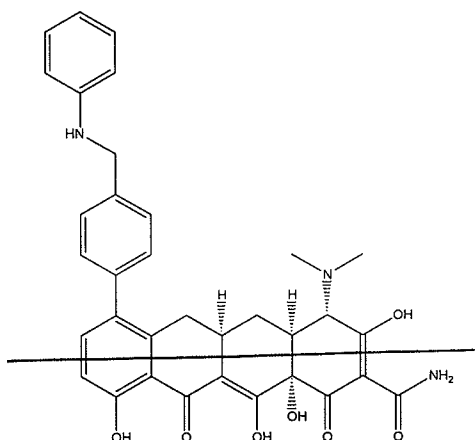
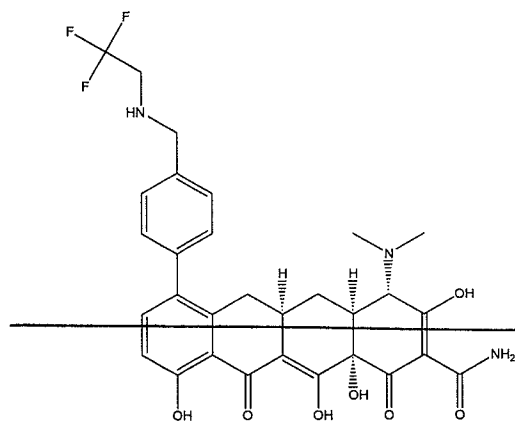
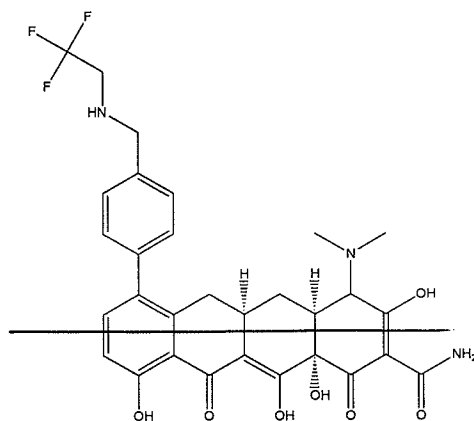
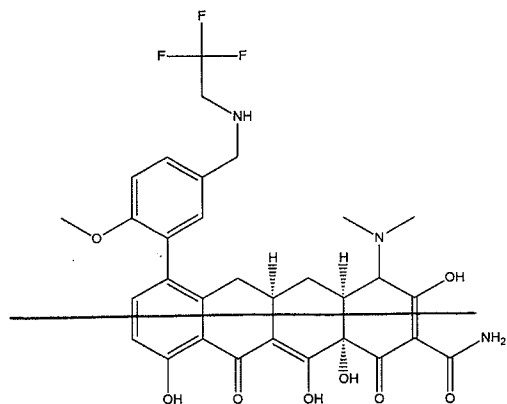


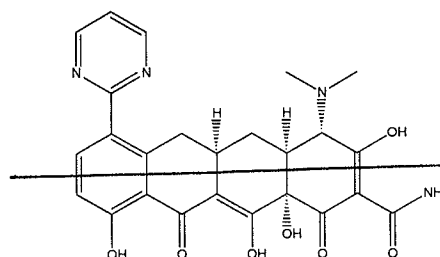
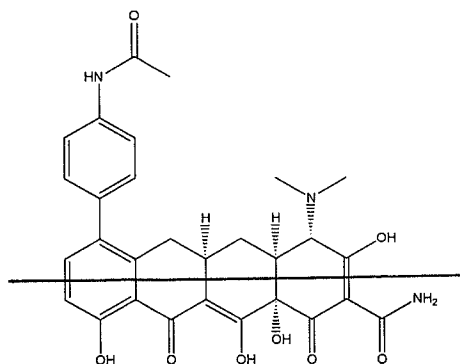
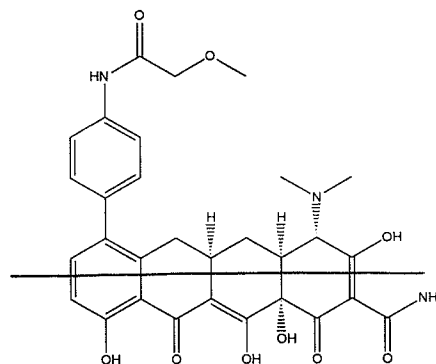
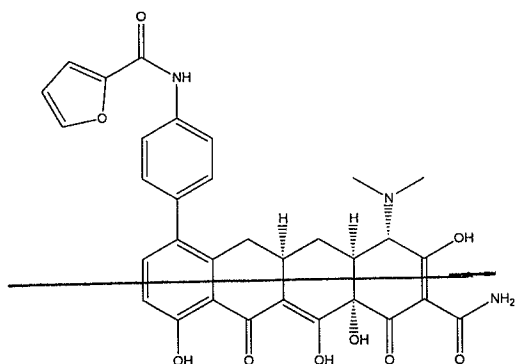
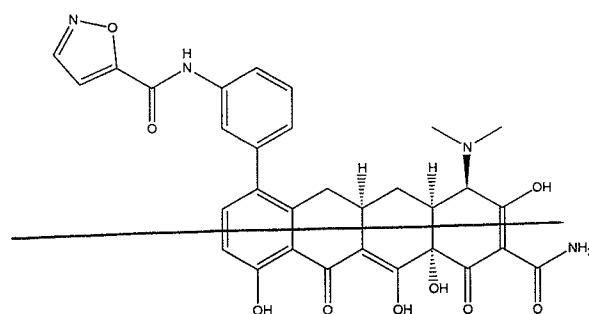
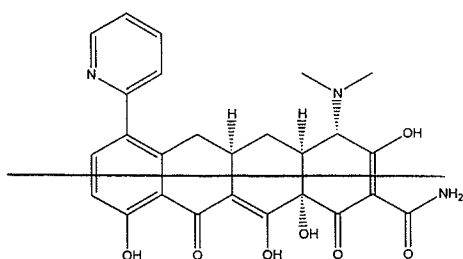
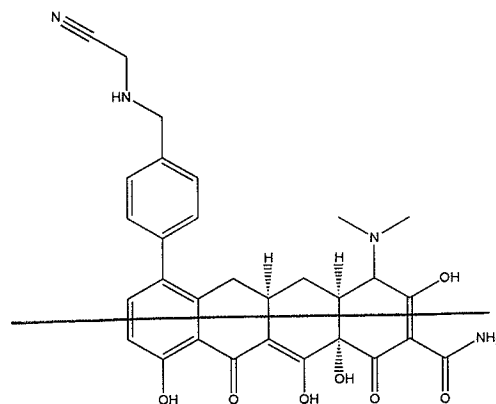
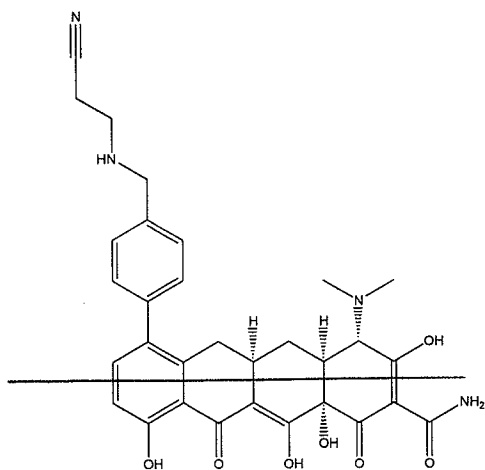


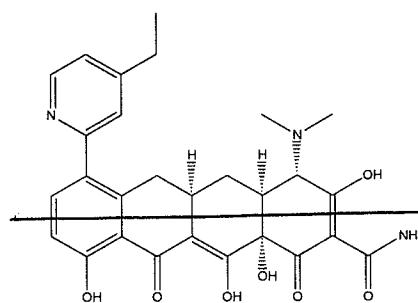
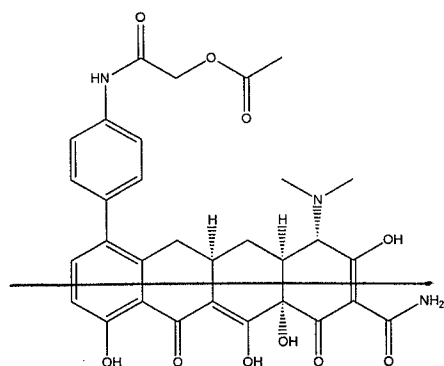
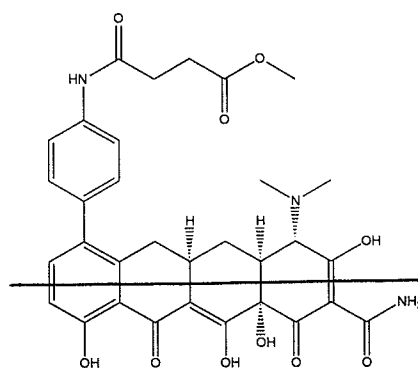
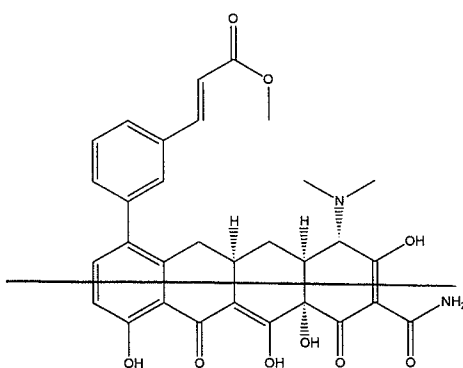
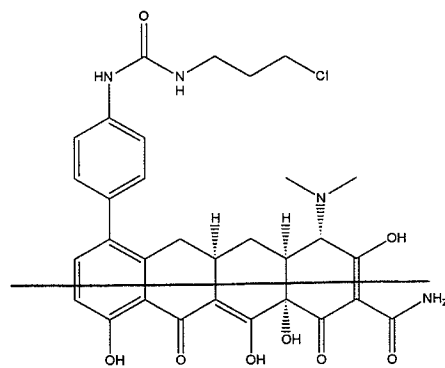
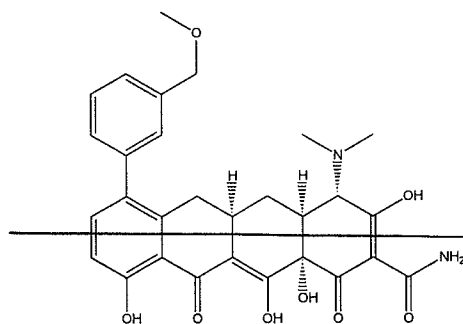
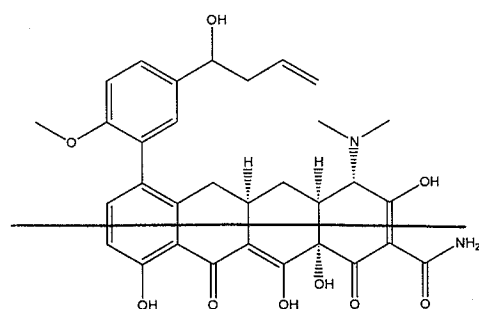
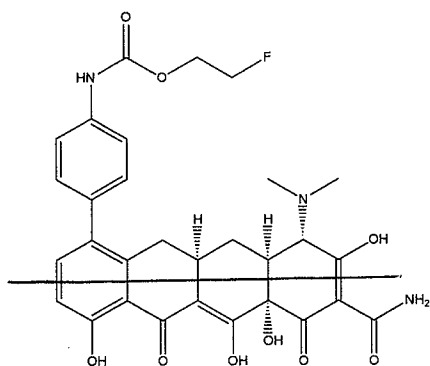


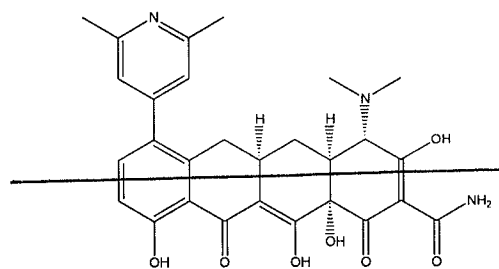
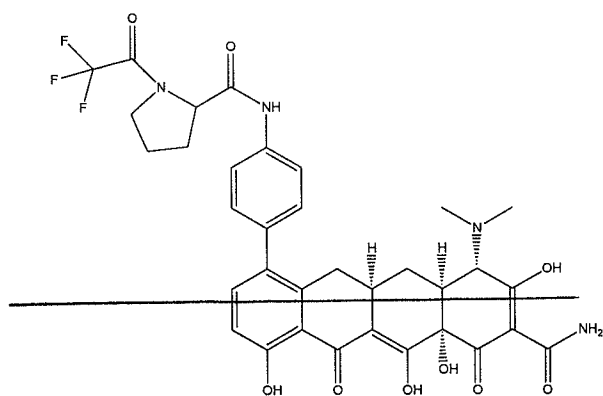
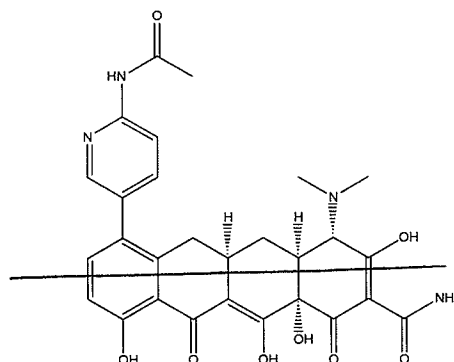
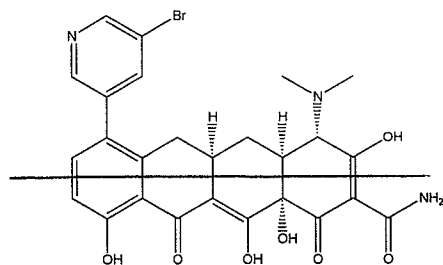
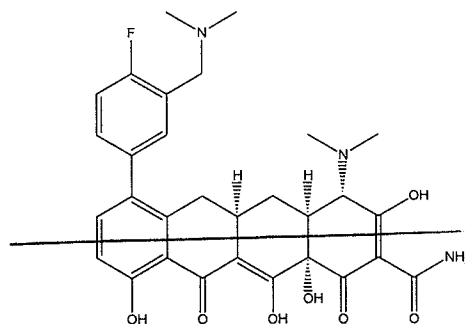
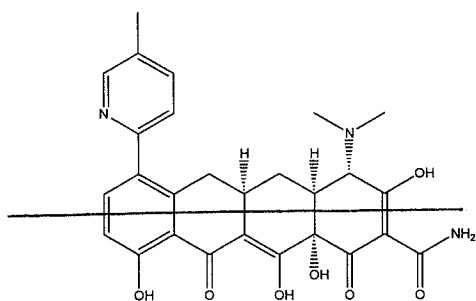
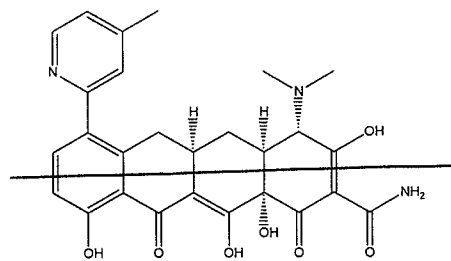
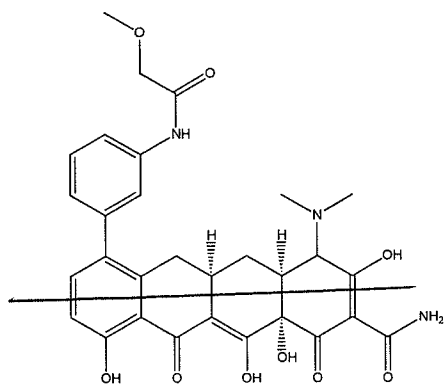


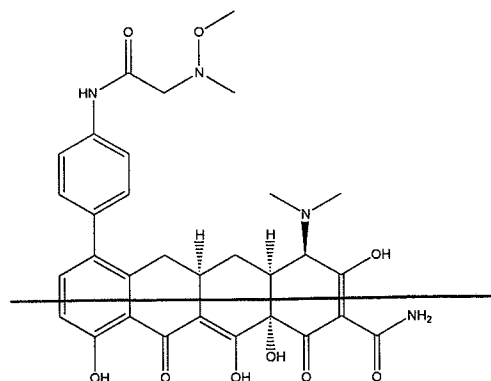
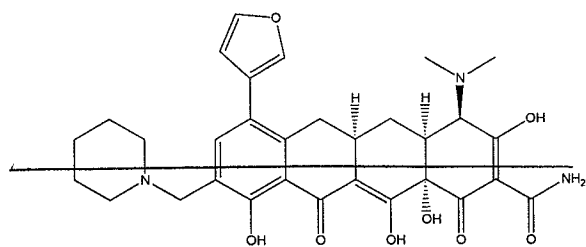
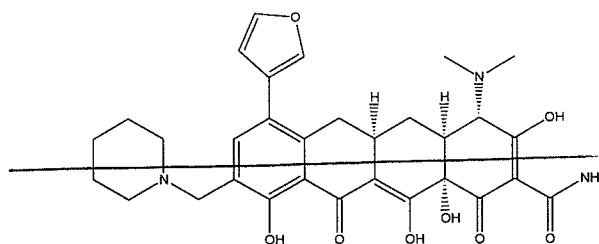
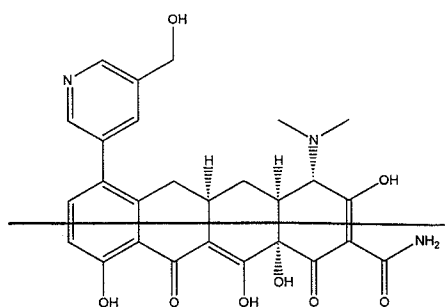
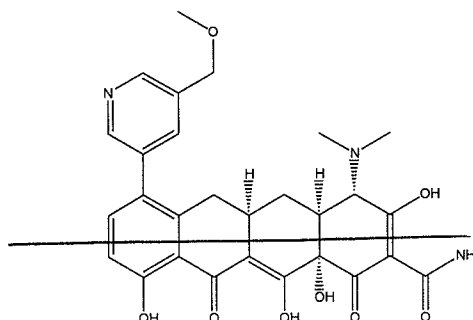
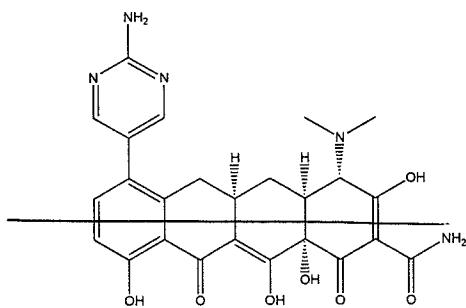
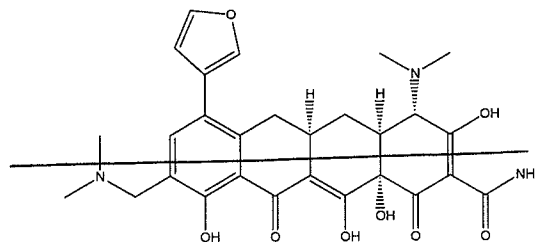
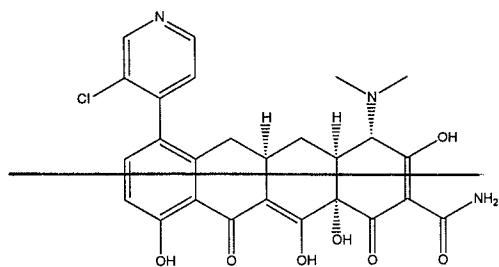


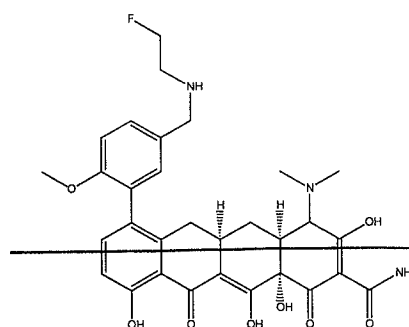
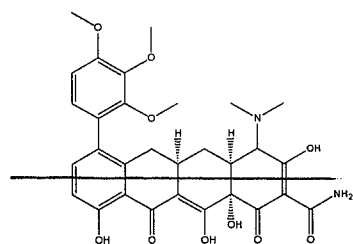
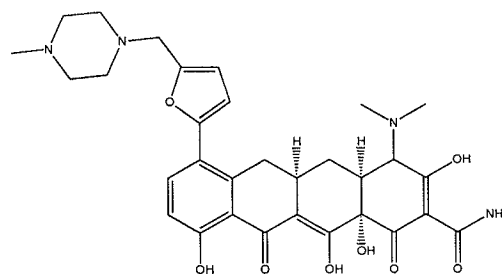
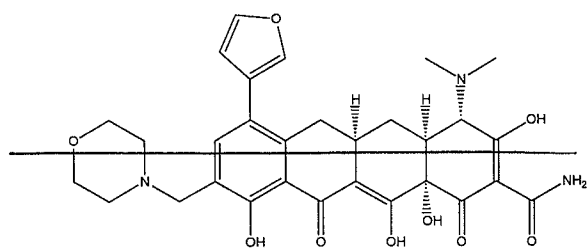
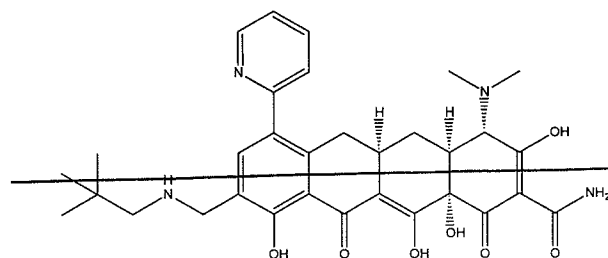
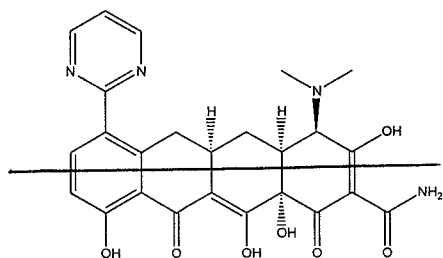
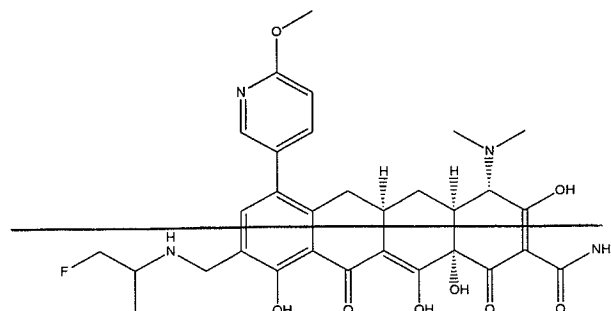
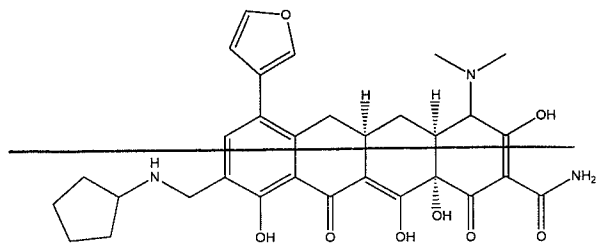
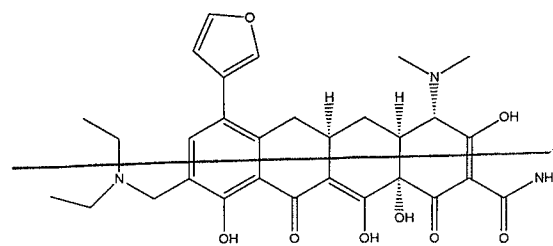
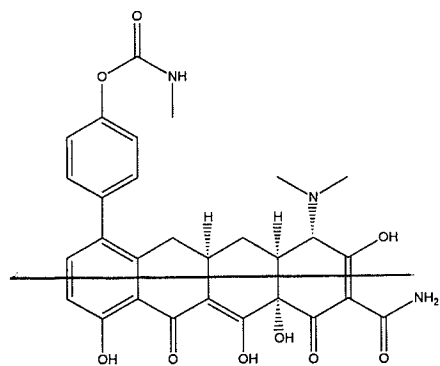


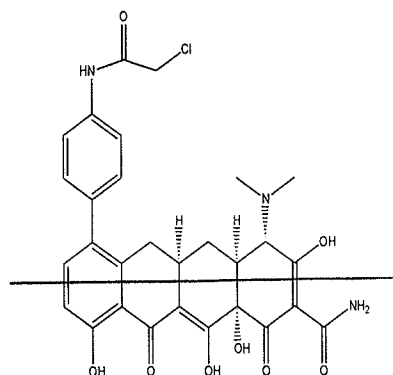
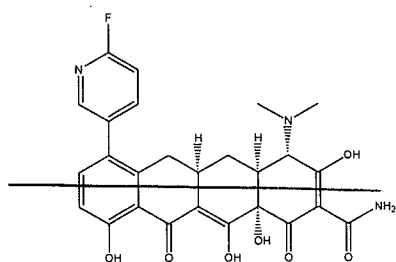
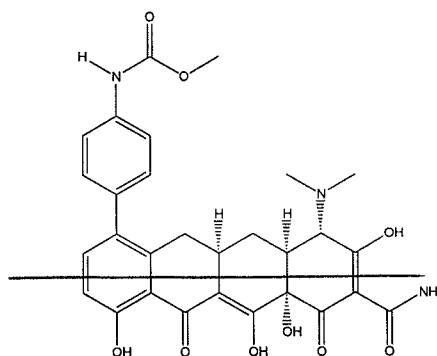
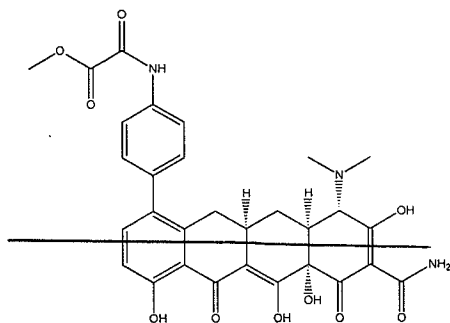
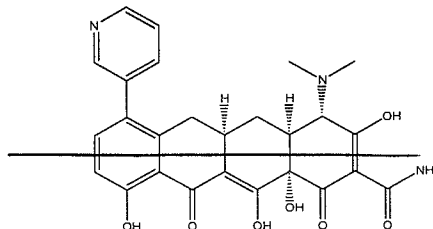
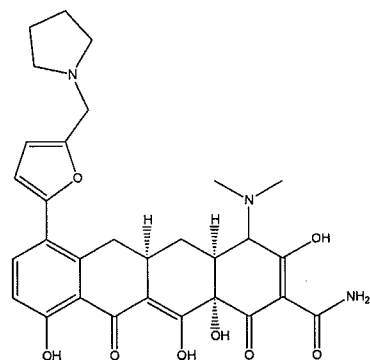
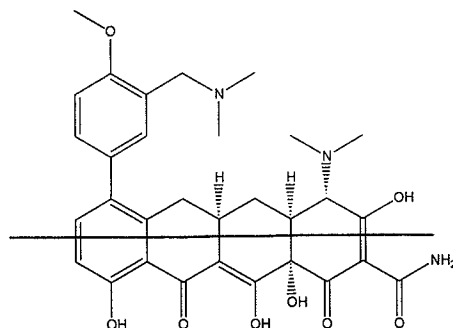
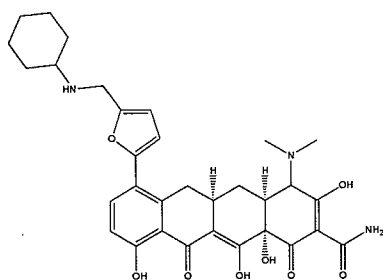


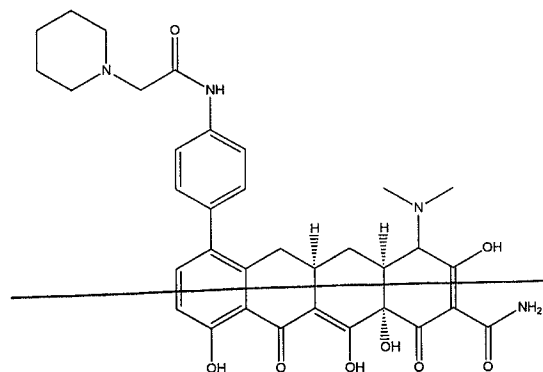
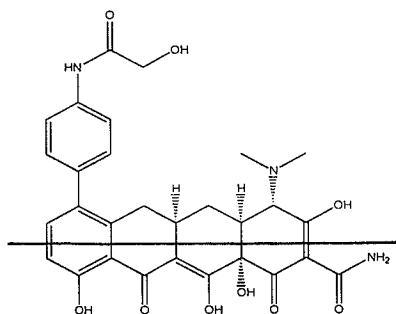
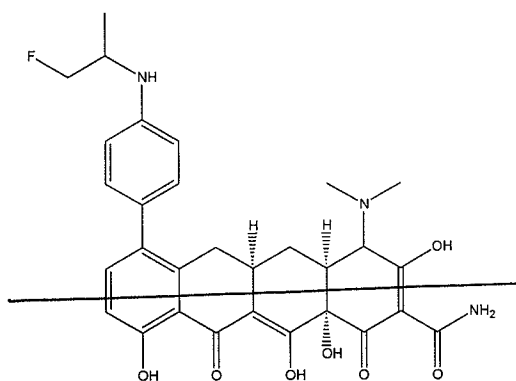
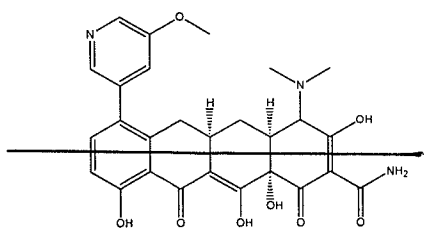
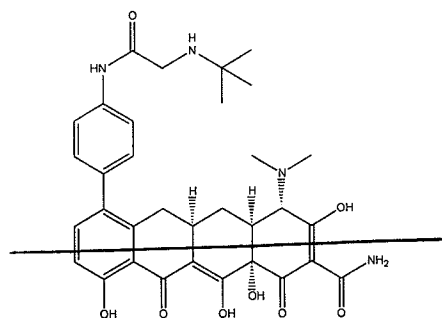
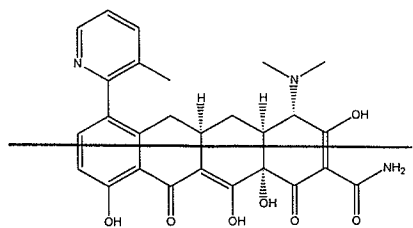
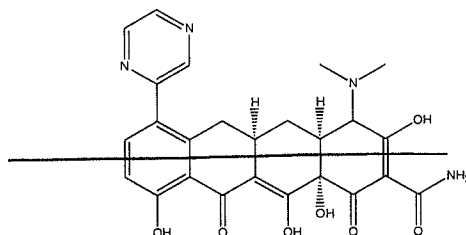
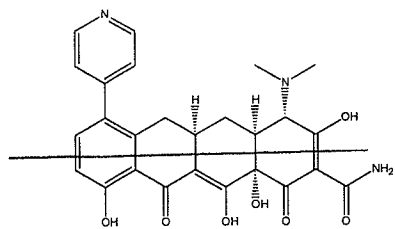


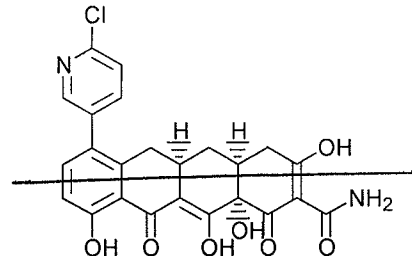
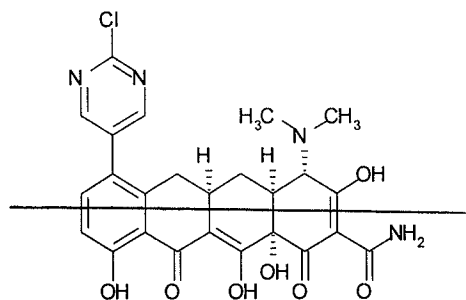
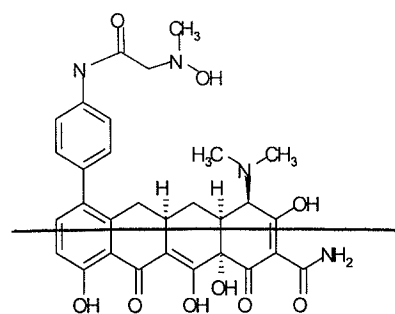
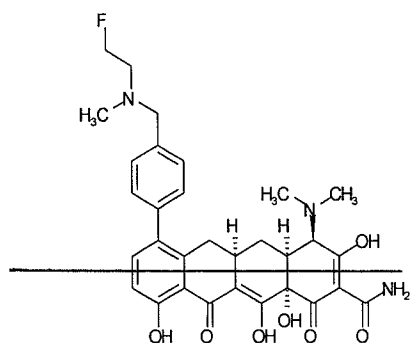
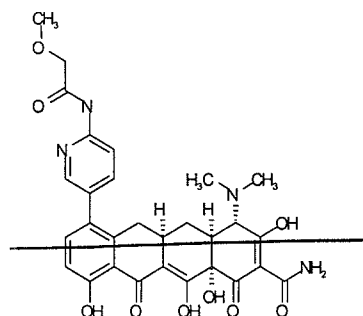
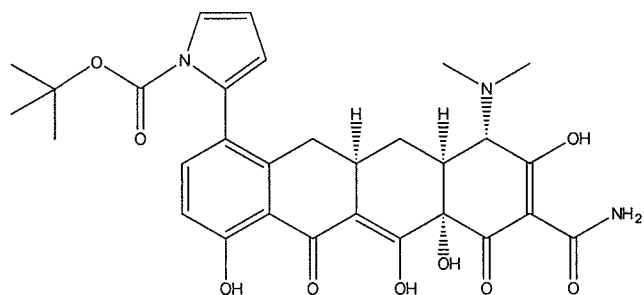
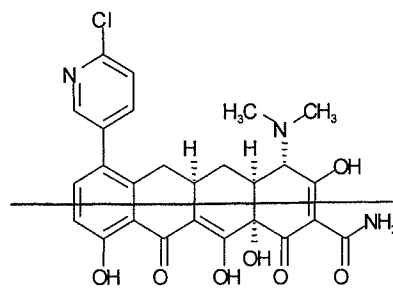
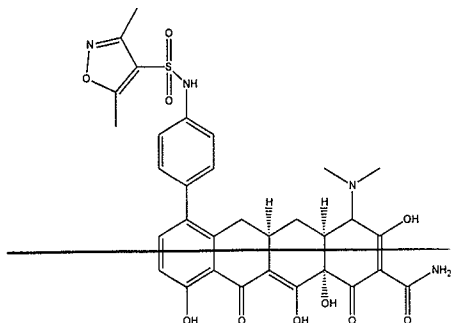
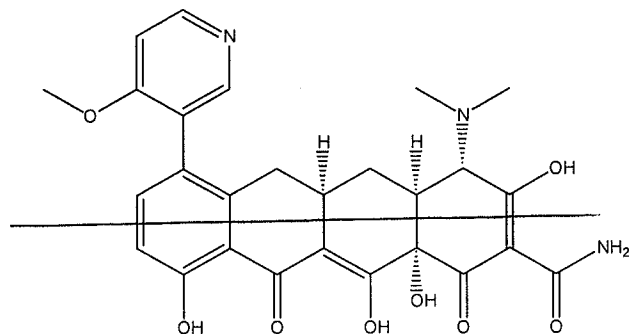
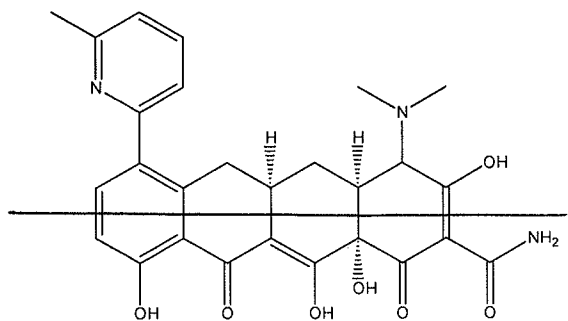


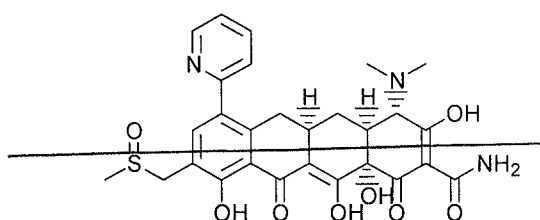
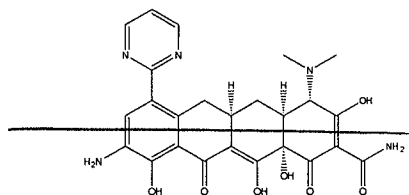
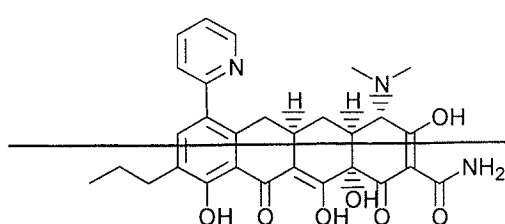
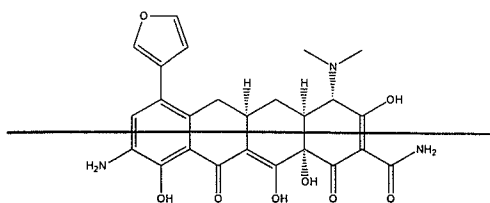
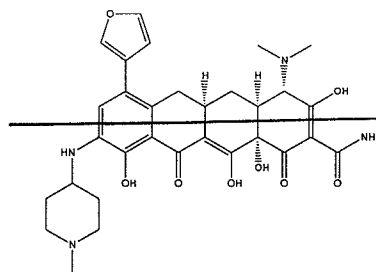
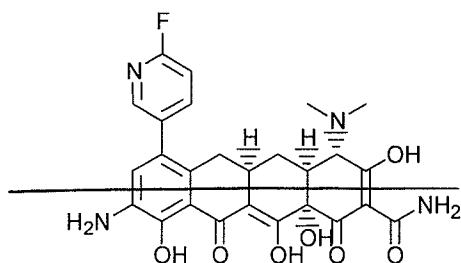
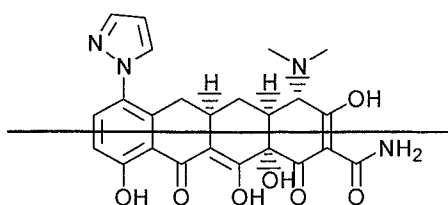
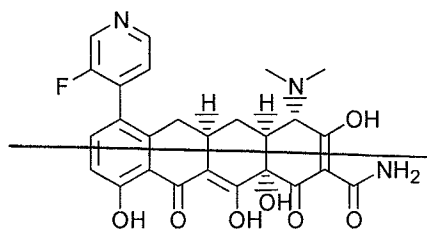
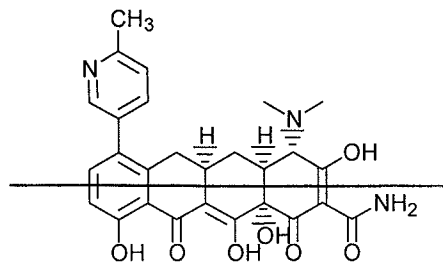
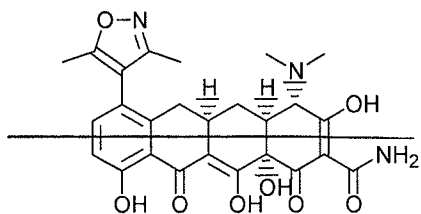


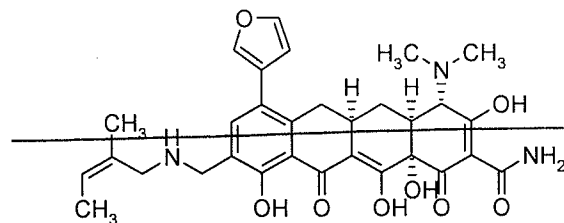
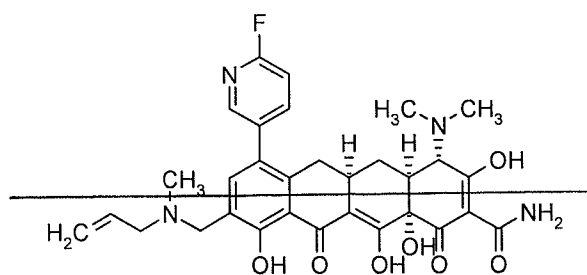
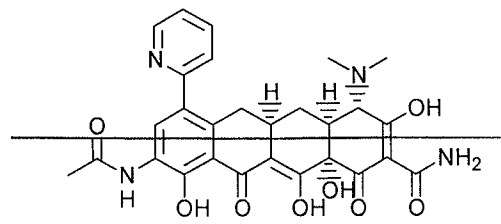
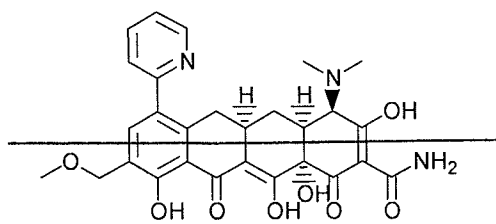
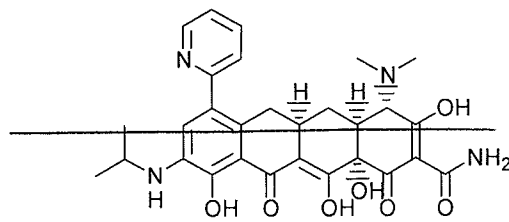
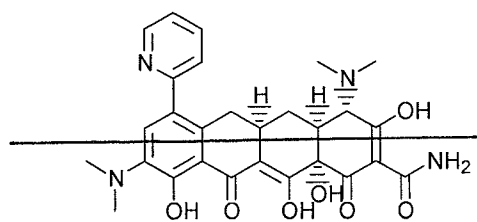
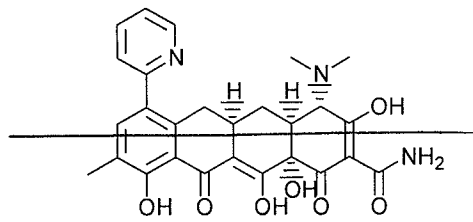
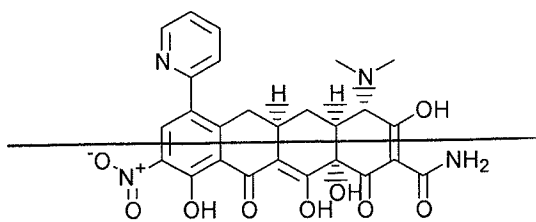
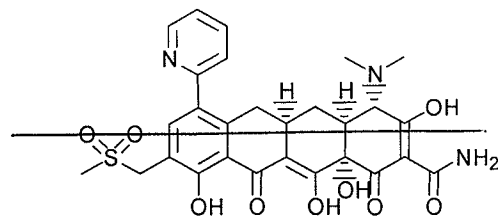
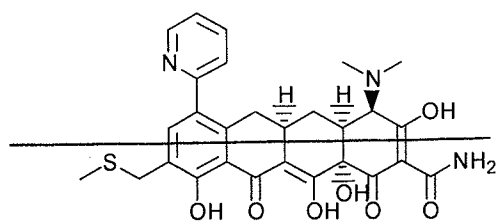


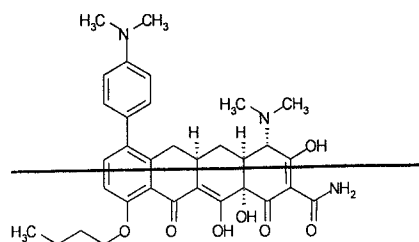
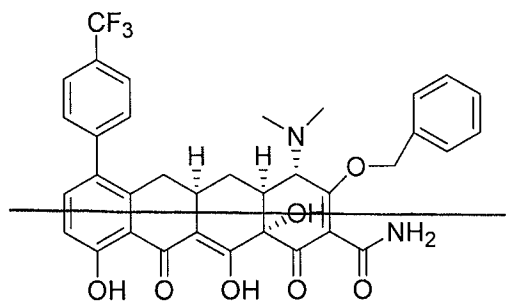
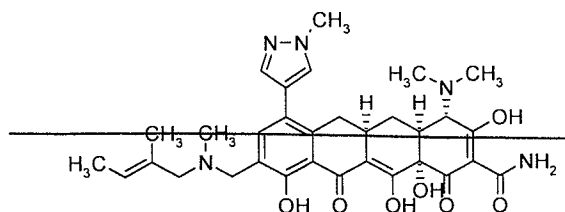
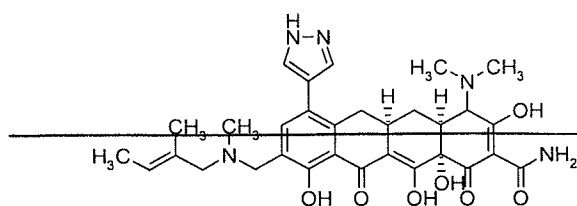
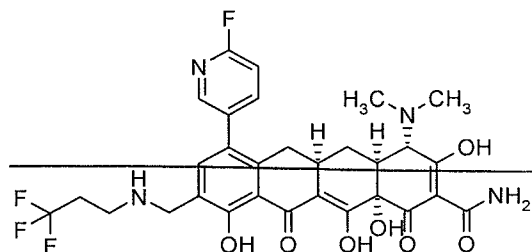
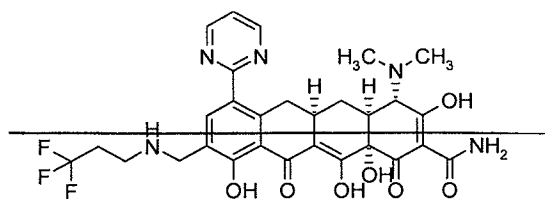
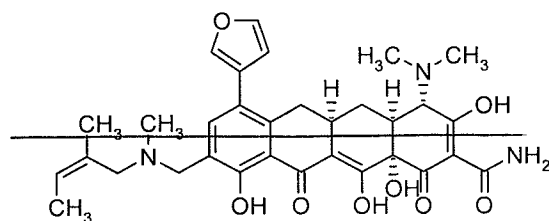
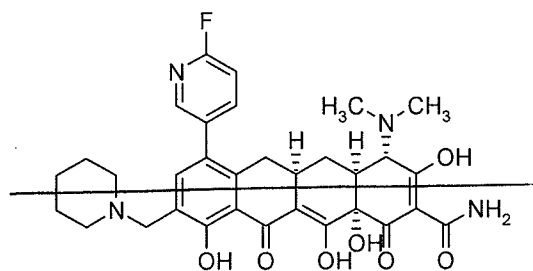


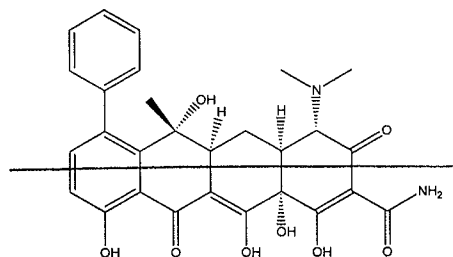
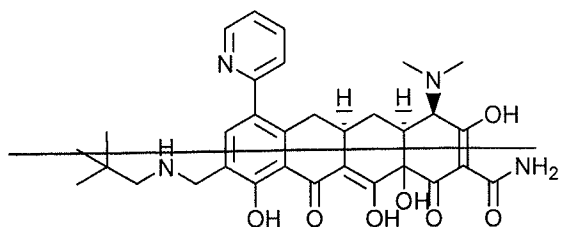
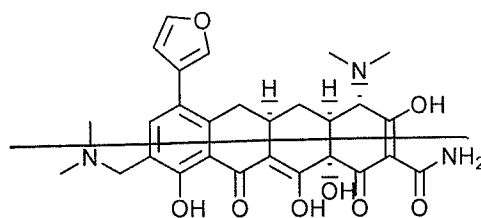
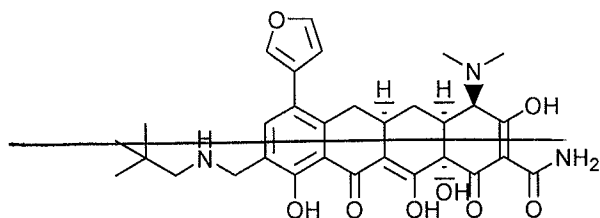
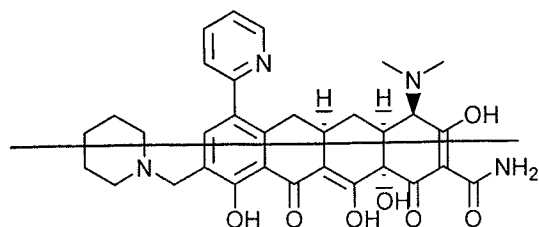
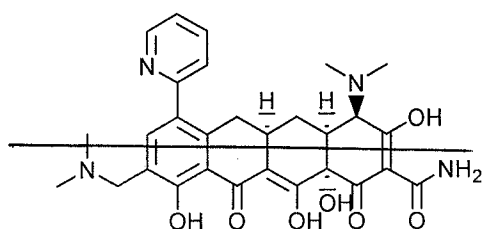
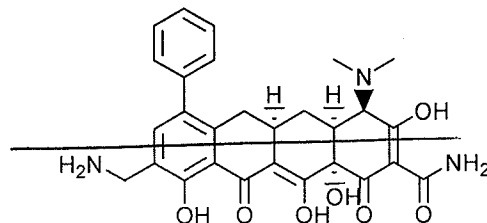
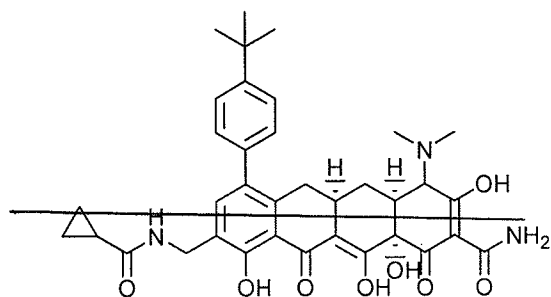
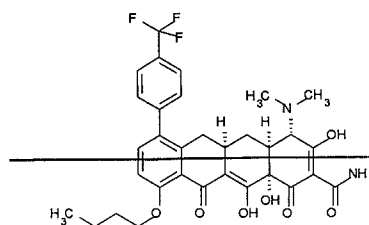
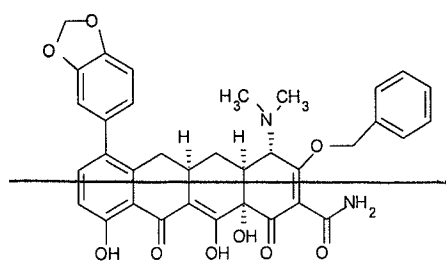


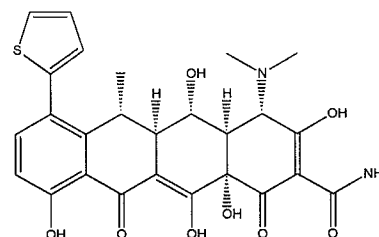
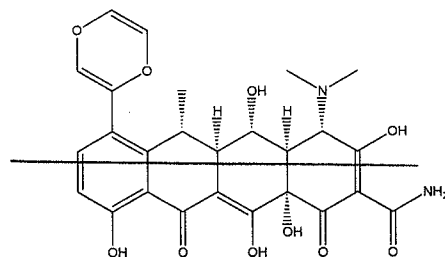
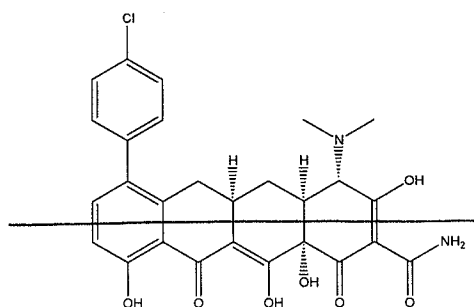
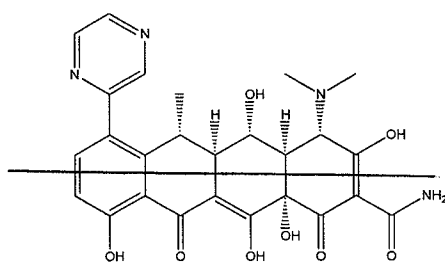
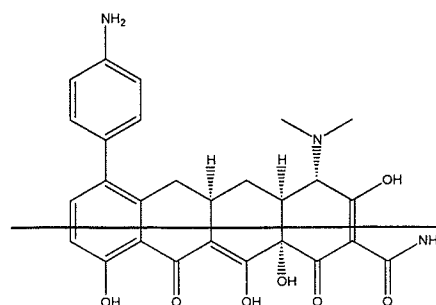
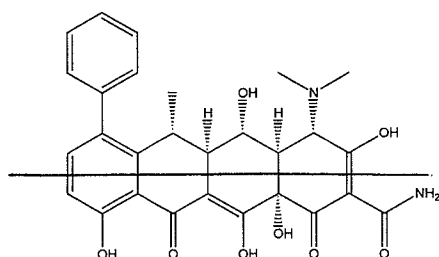
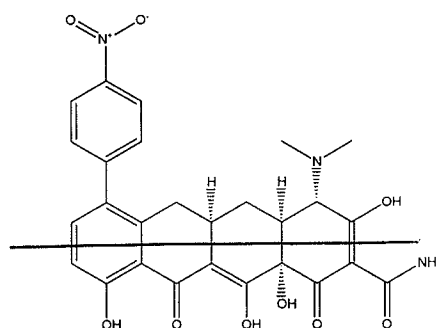
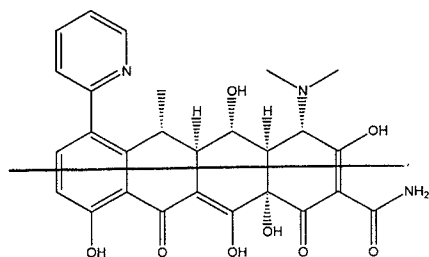
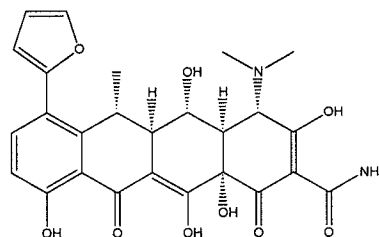
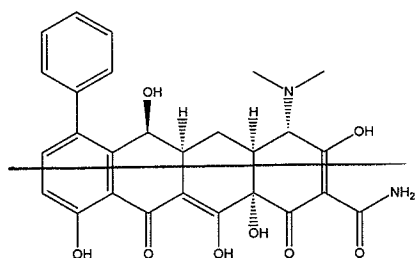


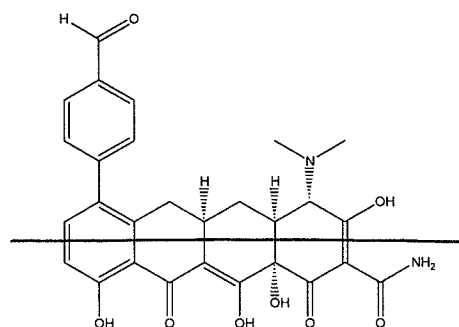
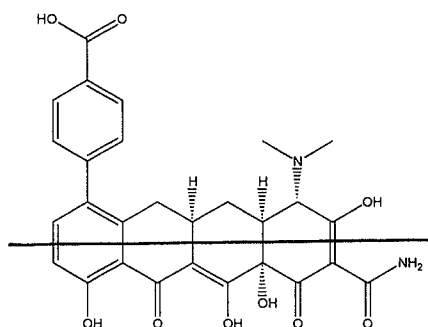
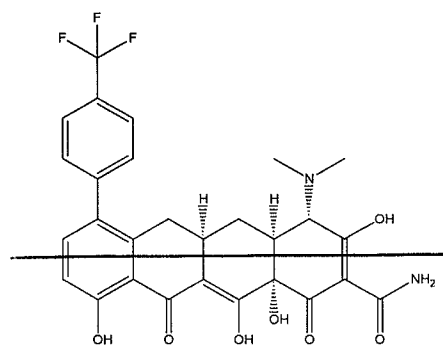
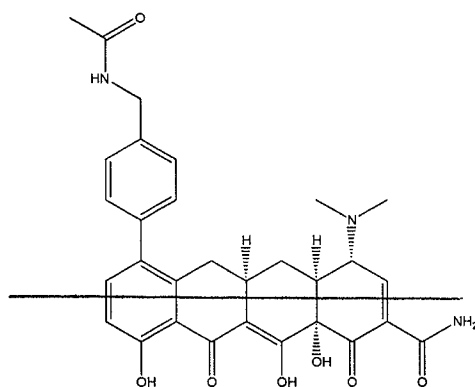
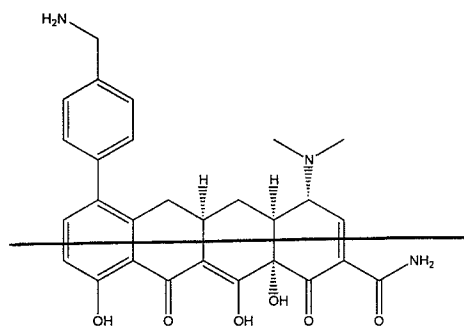
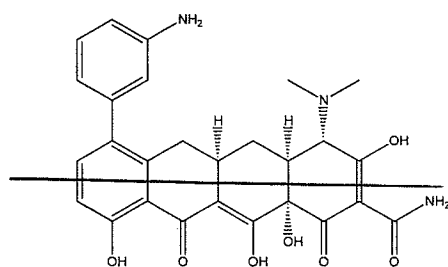
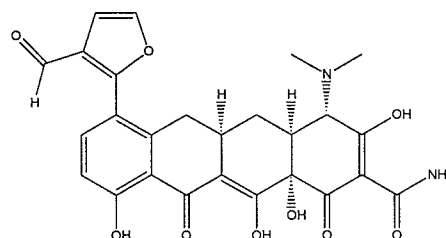
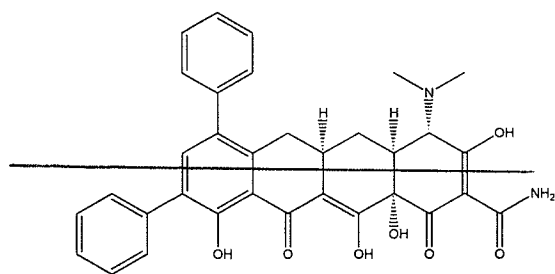
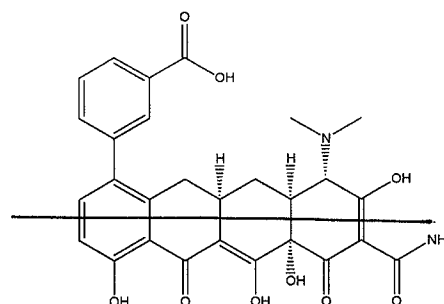
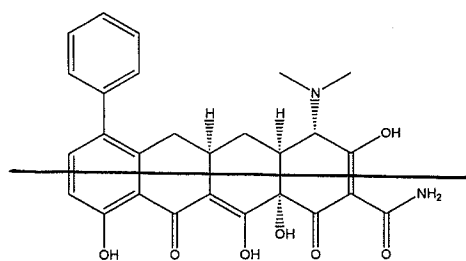


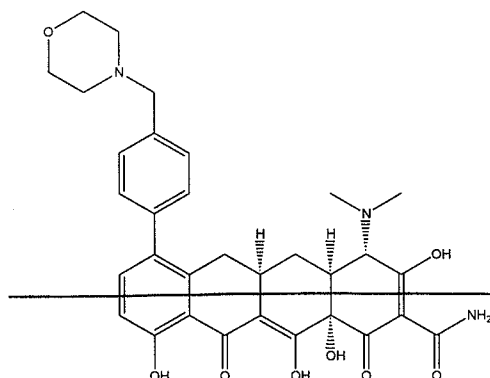
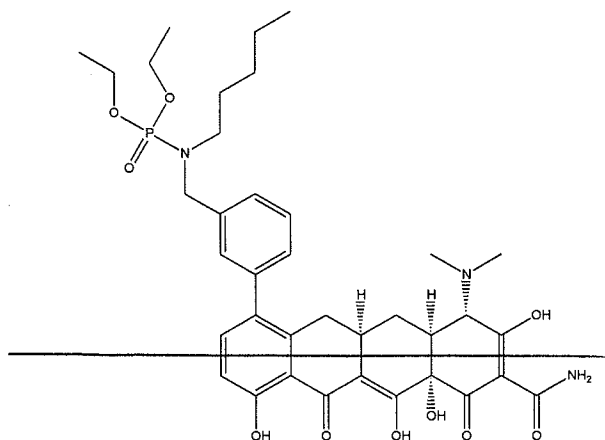
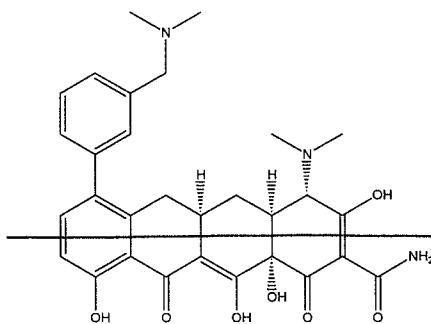
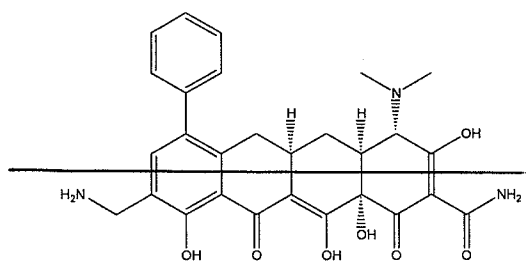
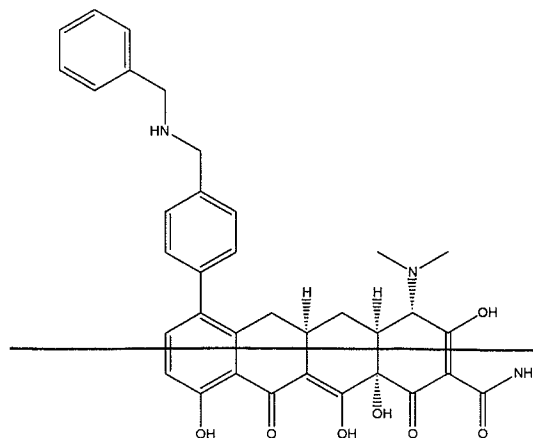
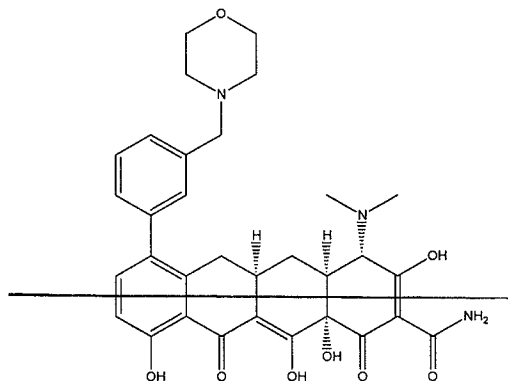
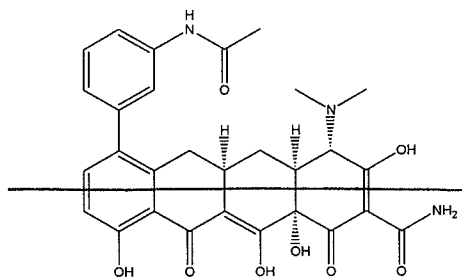
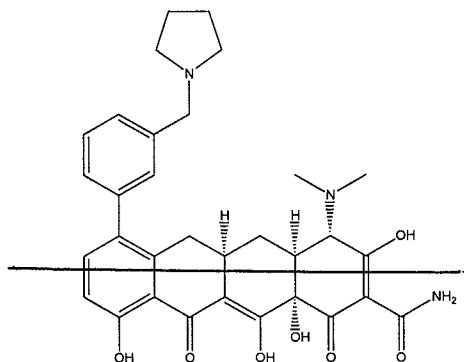


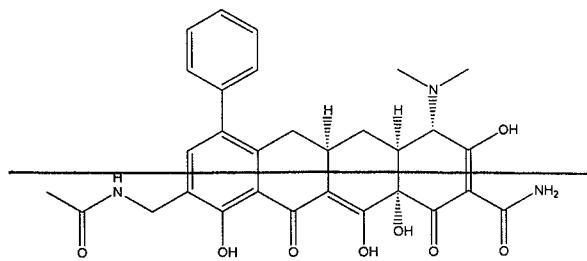
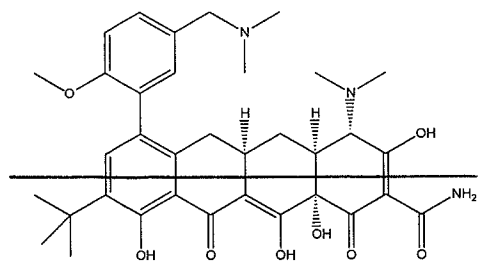
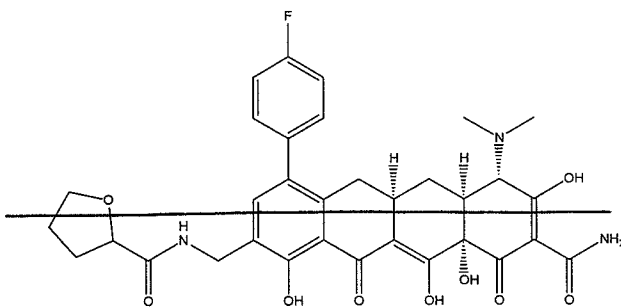
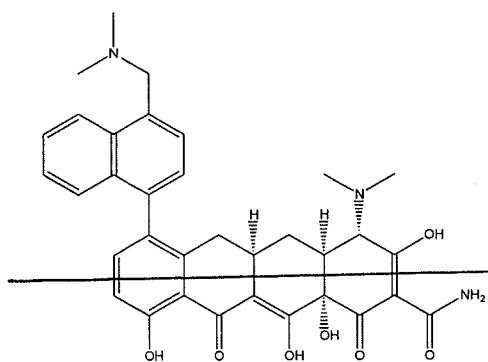
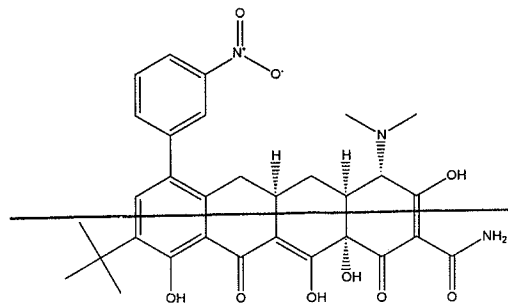
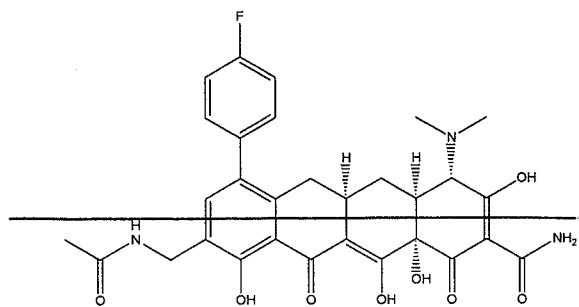
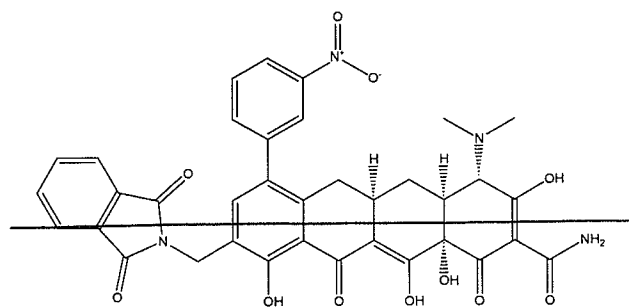
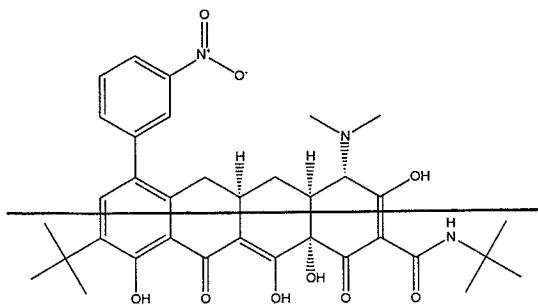


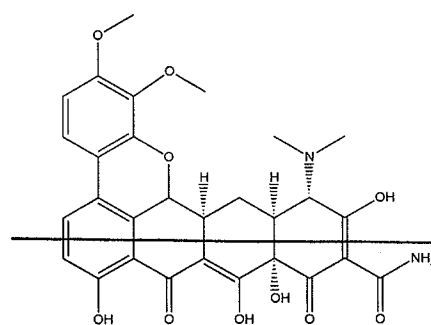
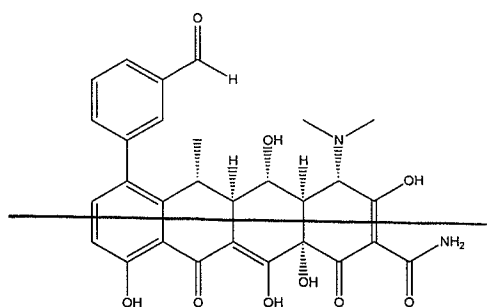
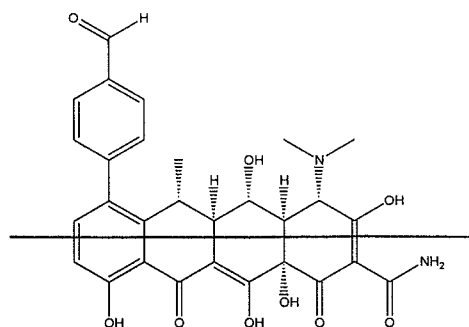
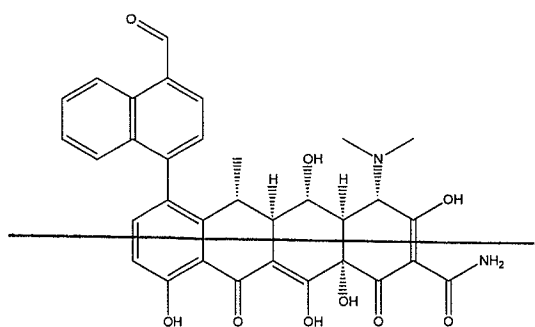
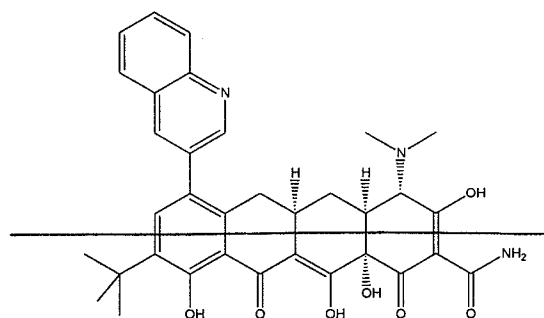
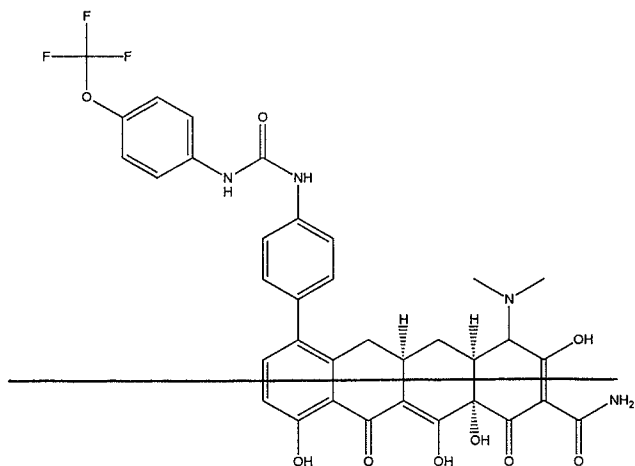
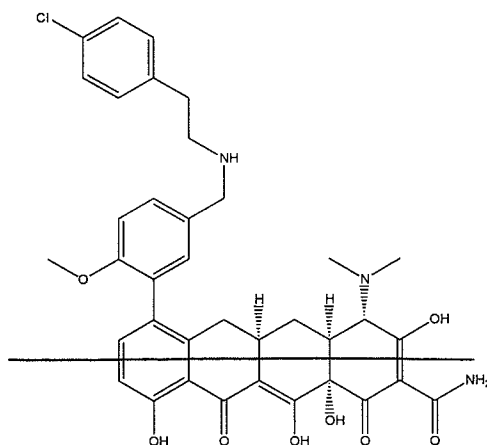
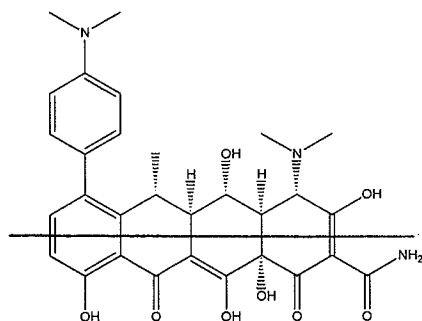


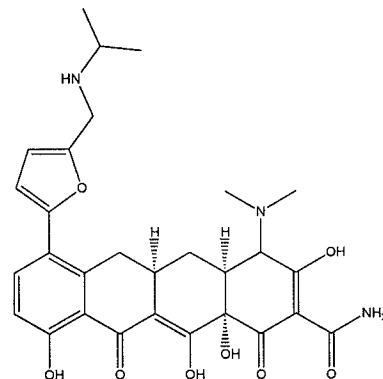
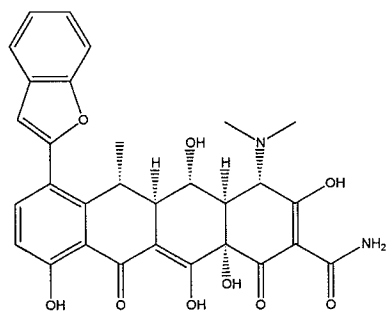
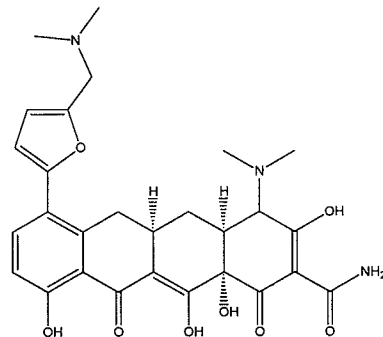
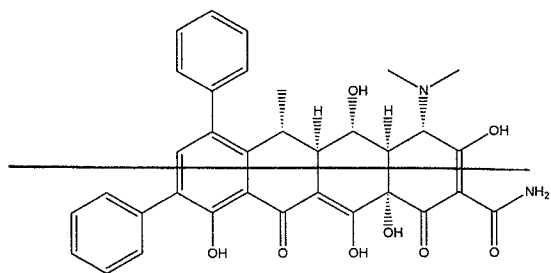
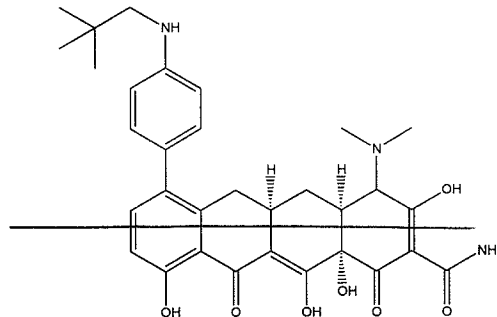
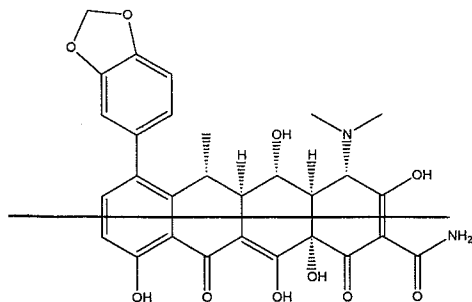
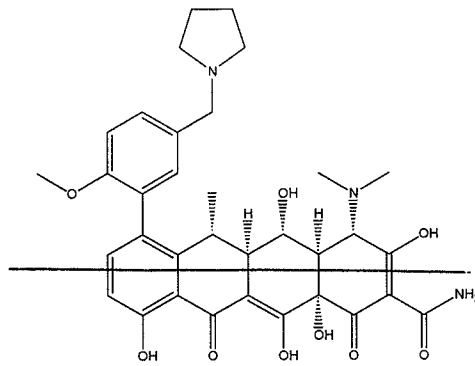
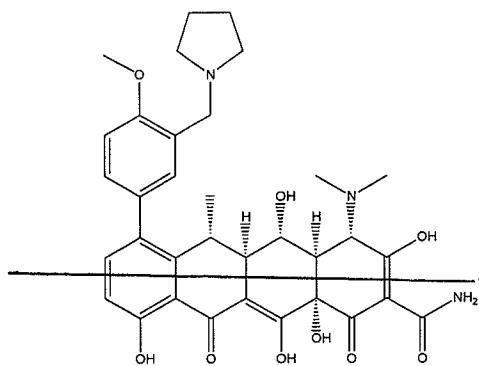


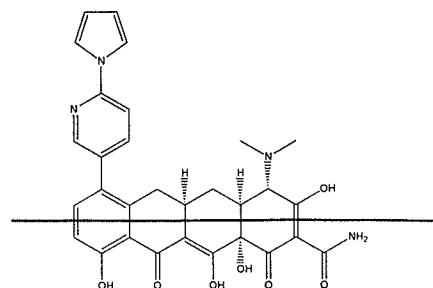
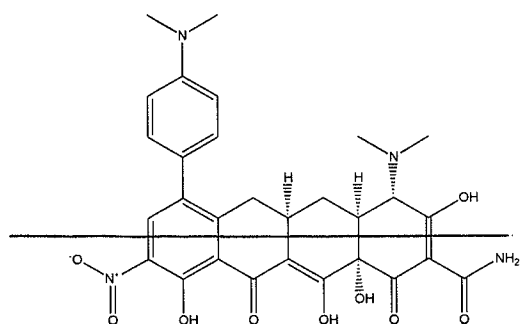
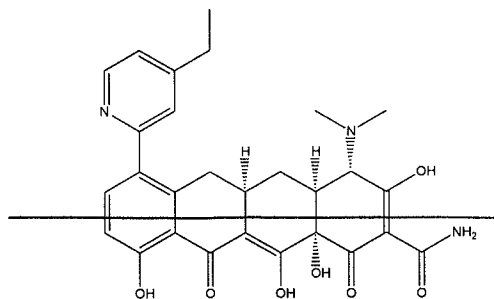
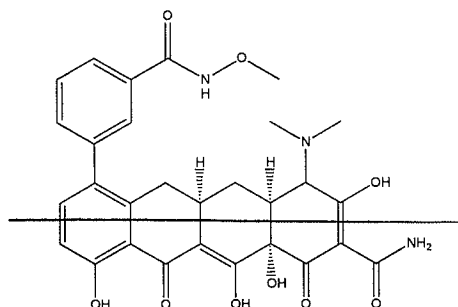
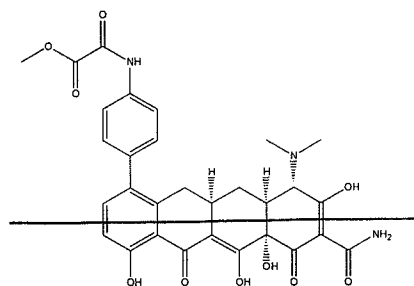
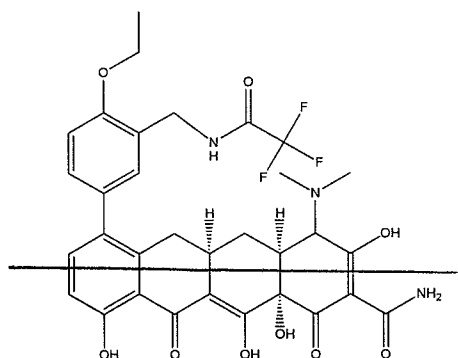
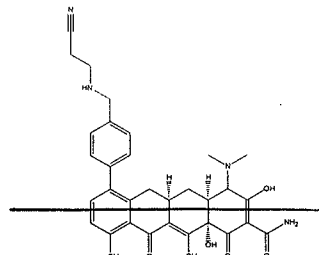
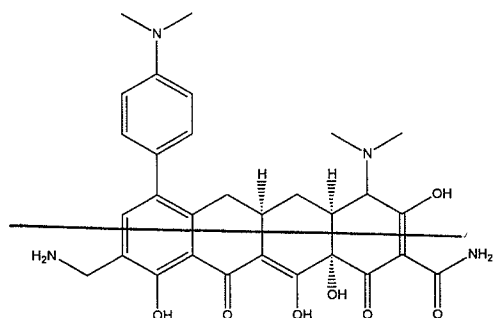
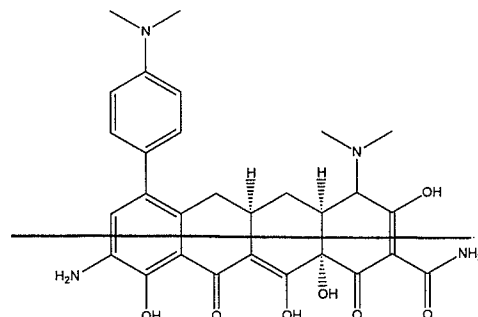
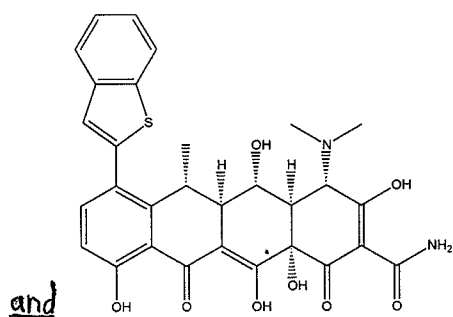


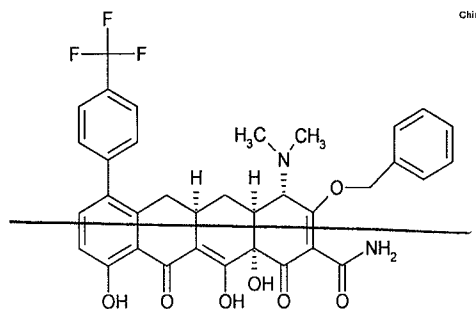
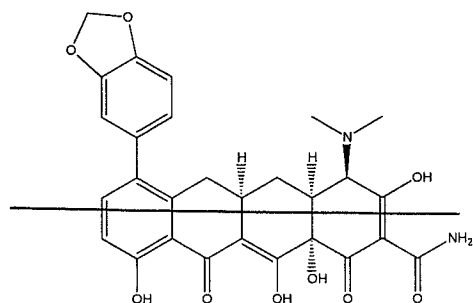




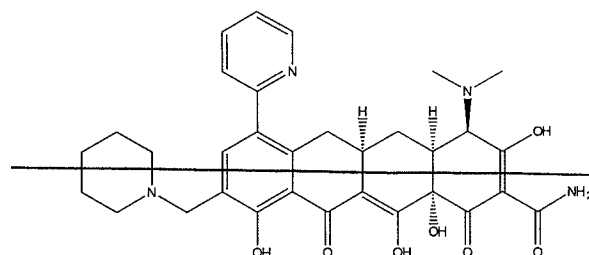
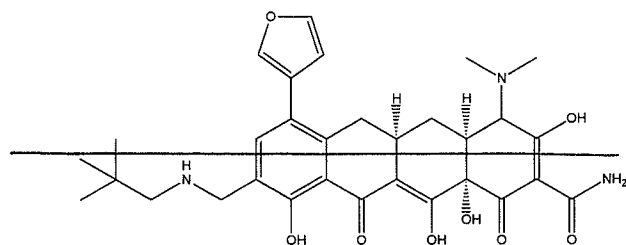




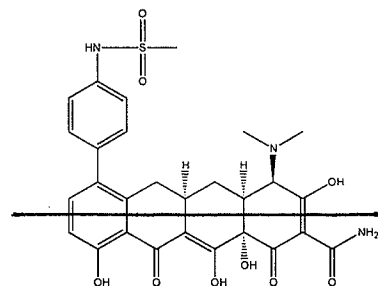
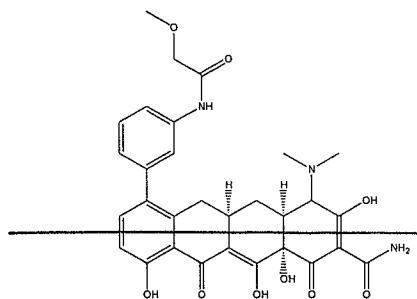
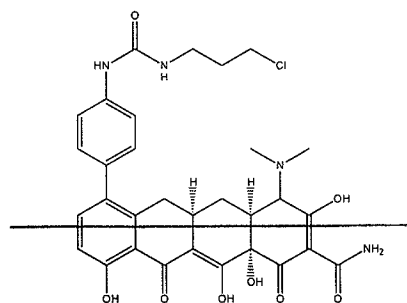
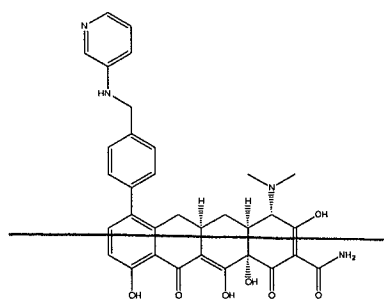
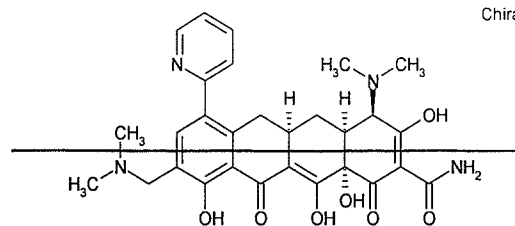
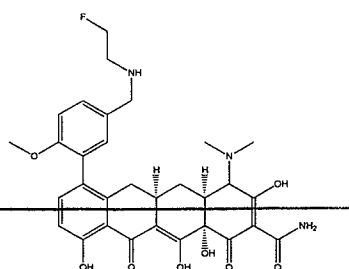




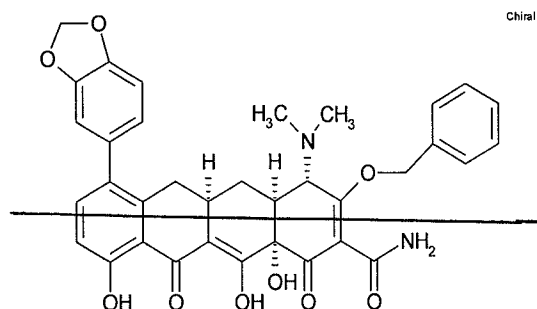
Chiral



Chiral



and



72. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is non-antibacterial.

73. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is has anti-microbial gram positive activity.

74. **(Original)** The method of claim 73, wherein said anti-microbial gram positive activity is greater than about 0.05 $\mu\text{g/ml}$.

75. **(Original)** The method of claim 74, wherein said anti-microbial gram positive activity is greater than about 5 $\mu\text{g/ml}$.

76. **(Original)** The method of claim 75, wherein said substituted tetracycline compound has a cytotoxicity of 25 $\mu\text{g/ml}$ or greater.

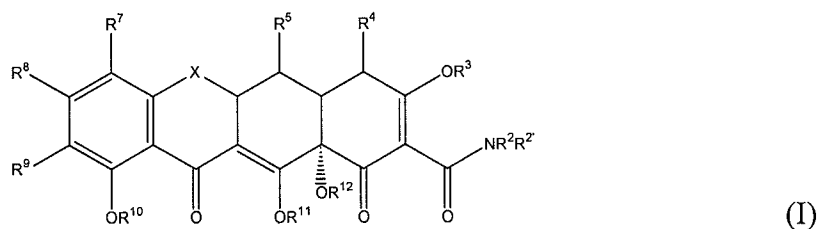
77. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound has a MIC of 150 nM or less.

78. **(Original)** The method of claim 77, wherein said substituted tetracycline compound has a MIC of 50 nM or less.

79. **(Original)** The method of claim 78, wherein said substituted tetracycline compound has a MIC of 10 nM or less.

80. **(Original)** The method of claim 79, wherein said substituted tetracycline compound has an MIC or 5 nM or less.

81. **(Currently Amended)** A pharmaceutical composition comprising an effective amount of a substituted tetracycline compound to treat malaria in a mammal and a pharmaceutically acceptable carrier, wherein said tetracycline compound is of formula I:



wherein:

X is CR^{6'}R⁶;

R², R^{2'}, R^{4'}, and R^{4''} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R⁴ is NR^{4'}R^{4''}, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R³, R¹¹ and R¹² are each hydrogen, or a pro-drug moiety;

R¹⁰ is hydrogen, or a prodrug moiety;

R⁵ is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

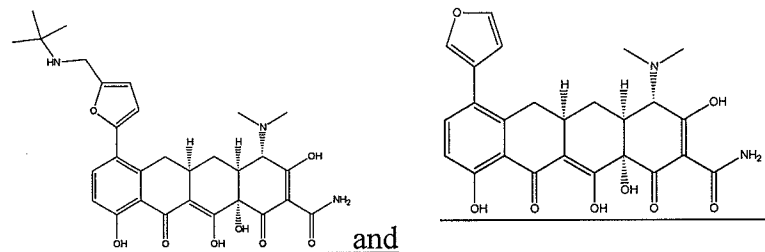
R⁶ and R^{6'} are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R⁷ is arylfuranyl, benzofuranyl, thienyl, benzothienyl, indolyl, or pyrrolyl;

R⁹ is hydrogen; and

R⁸ is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and pharmaceutically acceptable salts thereof.

82. **(Currently Amended)** The pharmaceutical composition of claim 81, wherein said substituted tetracycline compound is selected from the group consisting of:



83. (Canceled)

84. (Original) The pharmaceutical composition of claim 81, further comprising a secondary agent.

85. (Original) The pharmaceutical composition of claim 84, wherein the secondary agent is selected from the group consisting of proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide and pyronaridine.

86. (Canceled)

87. (Canceled)